27 March 2025
EMA/CHMP/136733/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Opdivo

International non-proprietary name: Nivolumab

Procedure No. EMEA/H/C/003985/II/0140

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
ADJ	adjuvant
AE	adverse event
ALT	anaplastic lymphoma kinase
atezo	atezolizumab
AUC	area under the plasma drug concentration-time curve
BICR	Blinded Independent Central Review
BIPR	Blinded Independent Pathological Review
BMS	Bristol-Myers Squibb
BSC	best supportive care
Cavg1	time-averaged concentration after the first dose
cCRT	concurrent chemoradiotherapy
chemo	platinum-doublet chemotherapy
cHL	Classic Hodgkin Lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CMH	Cochran-Mantel-Haenszel
CO	Clinical Overview
CRR	clinical response rate
CR	complete response
CRC	colorectal cancer
CRF	case report form
CSR	clinical study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumour DNA
DBL	database lock
DC	discontinuation
DFS	disease-free survival

DMC	data monitoring committee
dMMR	mismatch repair deficient
durva	durvalumab
EAC	oesophageal adenocarcinoma
EC	oesophageal cancer
ECOG	Eastern Cooperative Oncology Group
ECL	electrochemiluminescence
EFS	event-free survival
EFS2	event-free survival on next line of therapy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESCC	oesophageal squamous cell carcinoma
E-R	exposure-response
EU	European Union
FDA	Food and Drug Administration
GEJC	gastro-oesophageal junction cancer
GC	gastric cancer
HCC	hepatocellular carcinoma
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
Ig	Immunoglobulin
IMAE	immune-mediated adverse event
IMM	immune-modulating medication
IO	Immuno-oncology
Ipi	Ipilimumab
irAR	immune-related adverse reaction
IRF	Independent Review Facility
IRT	interactive response technology
ITT	Intent-to-treat
IV	intravenous
KM	Kaplan-Meier
mDFS	median disease-free survival

MedDRA	Medical Dictionary for Regulatory Activities
MPM	malignant pleural mesothelioma
MPR	major pathologic response
MSI-H	microsatellite instability-high
mos	months
NA	not available / not applicable
Neoadj	neoadjuvant
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
nivolumab	nivolumab
NR	not reached
NSCLC	non-small cell lung cancer
NSQ	non-squamous
OESI	other events of special interest
OR	odds ratio
ORR	objective response rate
OS	overall survival
pCR	pathologic complete response
PD-L1	programmed death ligand 1
pembro	pembrolizumab
PFS	progression-free survival
PK	pharmacokinetics
PopPK	population pharmacokinetics
PORT	postoperative radiotherapy
PRO	patient reported outcome
PS	performance status
PT	preferred term
QXW e	very X weeks
RCC	renal cell carcinoma
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SAP	statistical analysis plan

SCE	Summary of Clinical Efficacy
SCCHN	squamous cell carcinoma of head and neck
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SOC	standard of care
SQ	squamous
torip	toripalimab
TTDM	time to death or distant metastases
UC	urothelial carcinoma
US	United States
USPI	United States Prescribing Information
W&P	Warning and Precaution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 9 January 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include OPDIVO for the treatment of patients with resectable stage II-IIIB non-small cell lung cancer, based on results from study CA209977T; a phase 3, randomised, double-blind study of neoadjuvant chemotherapy plus nivolumab versus neoadjuvant chemotherapy plus placebo, followed by surgical resection and adjuvant treatment with nivolumab or placebo for participants with resectable stage II-IIIB non-small cell lung cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 36.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0432/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0432/2020 was completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Antonio Gomez-Outes Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	9 January 2024
Start of procedure:	27 January 2024
CHMP Rapporteur Assessment Report	28 March 2024
PRAC Rapporteur Assessment Report	28 March 2024
PRAC Outcome	11 April 2024
CHMP members comments	15 Apr 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 April 2024
Request for supplementary information (RSI)	25 April 2024
CHMP Rapporteur Assessment Report	10 July 2024
CHMP members comments	17 Jul 2024
Updated CHMP Rapporteur Assessment Report	19 July 2024
Request for supplementary information (RSI)	25 July 2024
CHMP Rapporteur Assessment Report	3 March 2025
CHMP members comments	17 March 2025
Updated CHMP Rapporteur Assessment Report	20 March 2025
CHMP opinion	27 March 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Resectable [Stage IIA (> 4 cm) to IIIB (T3N2 or T4N2)] non-small cell lung cancer (as per the AJCC Cancer Staging Manual 8th Edition).

State the claimed the therapeutic indication

Initially proposed indication

OPDIVO, in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment after surgical resection, is indicated for the treatment of adult patients with resectable non-small cell lung cancer.

Epidemiology and risk factors, screening tools/prevention

Lung cancer is the leading cause of cancer mortality worldwide (1.8 million, or 18% of all cancer deaths in 2020), with 2.2 million newly diagnosed cases, or 11.4% of all cancers diagnosed in 2020. In Europe, 477,534 new lung cancer cases and 384,176 deaths due to lung cancer were estimated to occur in the same year (Globocan 2020).

The primary risk factor for lung cancer is smoking tobacco, which accounts for most lung cancer-related deaths. The risk that smoking will lead to cancer is higher for people who smoke heavily and/or for a long time. Exposed non-smokers also have an increased relative risk of developing lung cancer (NCCN Guidelines v. 3.2022). Other possible risk factors for lung cancer include disease history (i.e., COPD), cancer history, family history of lung cancer, and exposure to other carcinogens. Occupational exposure to asbestos and radon are also significant risk factors for lung cancer (Padinharayil H. et al. 2023).

Clinical presentation, diagnosis and stage/prognosis

Non-small cell lung cancer (NSCLC) represents 80% to 85% of all lung cancers (Abernethy et al 2017; Cheema et al 2019). At initial diagnosis of NSCLC, 26% of patients present with Stage I, 8.3% with Stage II, 27.6% with Stage III, and 38.1% with Stage IV disease (Morgensztern D. et al. 2010). With enhanced lung cancer screening techniques, the percentage of patients diagnosed during the non-metastatic stages is expected to increase over time.

Despite the advances in improving outcome using neoadjuvant or adjuvant chemotherapy treatment options, the 5-year survival rate for patients remains low at 56% to 65% for patients with Stage II, and 24% to 41% for patients with Stage III disease (Goldstraw et al. 2016).

Management

Treatment options for patients with newly-diagnosed non-metastatic NSCLC depend on tumour resectability and patient operability. Key considerations include tumour characteristics and location, extent of nodal involvement, lung function, patient age and comorbidities.

Approximately 20% to 25% of NSCLC patients are candidates for potentially curative surgical resection (Datta D, Lahiri B. 2003) which remains the cornerstone of treatment gold standard of treatment for many patients with non-metastatic NSCLC, especially Stages I, II, IIIA, and selected patients with Stage IIIB disease (i.e., N2) (ESMO 2017).

NCCN guidelines recommend that patients with stage IB (T2a, N0) to IIIA (T1-2, N2; T3, N1) disease (per the 8th edition American Joint Committee on Cancer/Union for International Cancer Control [AJCC/UICC] staging criteria) who had complete resection should receive adjuvant chemotherapy. According to ESMO Guidelines, adjuvant chemotherapy is of benefit for patients with N1 and N2 disease (stage II and III), resulting overall in 4%–5% absolute survival improvement at 5 years. However, its value in lower stages is less clear: for stage IA, postoperative chemotherapy resulted in a worse outcome; whereas for stage IB, a small overall benefit was found (mainly due to the outcome in patients with tumours > 4 cm) (ESMO 2017).

Neoadjuvant chemotherapy has not been evaluated as extensively as postoperative. However, comparing outcomes of both modalities did not reveal a major difference in OS (ESMO 2017). Using indirect comparison meta-analysis of 32 randomized trials, the relative HRs for OS and DFS with adjuvant chemotherapy compared with neoadjuvant chemotherapy were 0.99 (95% CI: 0.81, 1.21; p = 0.91) and 0.96 (95% CI: 0.77, 1.20; p = 0.70), respectively (Lim E. et al. 2009).

Regarding immunotherapies for the perioperative setting in resectable NSCLC in the EU, several studies are ongoing or have recently published results that showed improved clinical outcomes with perioperative treatment regimen in subjects with resectable Stage II, IIIA or IIIB NSCLC (KEYNOTE-671, AEGEAN, NeoTorch).

Opdivo (nivolumab), was granted an extension of indication in resectable NSCLC, as neoadjuvant treatment (EMEA/H/C/003985/II/0117, dated 26 June 2023), and Keytruda (pembrolizumab) and Tecentriq (atezolizumab), as adjuvant treatment (EMEA/H/C/003820/II/0110 dated 19 May 2022 and EMEA/H/C/004143/II/0064 dated 07 June 2022).

In March 2024, the CHMP adopted a positive opinion (EMEA/H/C/003820/II/0134) for a new indication for Keytruda (pembrolizumab) in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, for the treatment of resectable NSCLC at high risk of recurrence in adults.

In February 2025, the CHMP adopted a positive opinion (EMEA/H/C/004771/II/0064) for a new indication of Imfinzi (durvalumab) in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by Imfinzi as monotherapy as adjuvant treatment, for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements.

Unmet medical need

Despite the improved efficacy demonstrated in resectable NSCLC in either the neoadjuvant or the adjuvant setting, there is an unmet medical need to further improve clinical outcomes in this population.

The combination of both neoadjuvant and adjuvant therapies has the potential for improved outcomes, combining the role of neoadjuvant to induce immune system priming while the tumour is present, and for both adjuvant and neoadjuvant phases to target micrometastatic disease both prior and post-surgery with a potential for a long-term benefit.

2.1.2. About the product

Opdivo (nivolumab) is a human IgG4 monoclonal antibody and PD-1 immune checkpoint inhibitor. Nivolumab binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. Tumours use PD-L1 expression as a defence or escape mechanism against the host's anti-tumour T-cell response; therefore, by inhibiting PD-(L)1, the function of these anti-tumour T-cells which have become ineffective/suppressed is restored.

In the EU, nivolumab as a single agent has been approved for different indications, including melanoma, NSCLC, renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), and oesophageal cancers.

Nivolumab and ipilimumab combination therapy has been approved in the EU for the treatment of melanoma, RCC, malignant pleural mesothelioma, colorectal cancer (CRC) and oesophageal squamous cell carcinoma (OSCC) and hepatocellular carcinoma (HCC).

Nivolumab in combination with chemotherapy has been approved for gastric cancer, gastroesophageal junction cancer, and oesophageal adenocarcinoma.

Focusing on advanced/metastatic NSCLC, nivolumab is approved for the following indications:

- Opdivo in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

- Opdivo as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

Additionally, nivolumab is approved for the neoadjuvant treatment of resectable NSCLC, based on the results of pivotal Study CA209816. This indication reads as follows: OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥1%.

The indication applied for was:

OPDIVO, in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment after surgical resection, is indicated for the treatment of adult patients with resectable non-small cell lung cancer.

The final approved indication is:

OPDIVO, in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD L1 expression ≥ 1% (see section 5.1 for selection criteria).

Proposed dosage and administration

The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for up to 4 cycles in the neoadjuvant phase, followed after surgery by nivolumab 480 mg every 4 weeks in the adjuvant phase. Treatment is recommended until disease progression or recurrence, unacceptable toxicity, or up to 13 cycles in patients without disease progression.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The non-metastatic NSCLC program of nivolumab consists of 4 Phase 3 clinical studies, which investigate the potential role of nivolumab (± ipilimumab, chemotherapy, or chemoradiotherapy) as neoadjuvant, adjuvant, peri-operative, or concurrent chemoradiotherapy (CCRT) add-on treatment options. These are summarised in Table 1 below.

Table 1. Nivolumab clinical development program in non-metastatic NSCLC

	CA20977T	CA209816	CA209427[a]	CA20973L
Type of therapy	Neoadjuvant + adjuvant	Neoadjuvant	Adjuvant	Add to cCRT
Primary Population	Stage IIA (> 4 cm) to IIIB (T3N2 or T4N2) NSCLC	Stage IB (≥ 4 cm) – IIIA NSCLC	Stage IB (≥ 4 cm) - IIIA NSCLC	Locally advanced Stage IIIA, IIIB, or IIIC (T1-2 N2-3 M0, T3 N1-3 M0, or T4 N0-3 M0) histologically-confirmed NSCLC
Study Status	Enrollment complete; Primary analysis completed	Enrollment complete; Primary analysis completed	Enrollment complete; data pending	Enrollment complete; data pending
Treatment	Nivo + Chemo then Nivo; Chemo then Observation	Nivo + Chemo; Chemo; Nivo + Ipi	Nivo; Observation	Nivo + cCRT then Nivo + Ipi; Nivo + cCRT then Nivo; cCRT then Durva
Cancer Stage	8th edition	7th edition	7th edition	8th edition
IB (> 4 cm)		√	√	
II	√	√	√	
IIIA	√	√	√	√
IIIB	√			√
IIIC				√
Efficacy Endpoints[b]				
OS	√	√	√ (Primary)	√
EFS	√ (Primary)	√ (Primary)		
PFS				√ (Primary)
DFS			√ (Primary)	
TTDM	√	√		√
pCR rate	√	√ (Primary)		
MPR rate	√	√		
ORR	√ [c]	√ [c]		√
CR rate				√
DOR				√
TTR				√

[a] ANVIL: A Phase 3 non-BMS-sponsored (ECOG) research study of registrational intent. Primary endpoint is event-driven and data are not available to BMS.

[b] Exploratory endpoints are not included.

[c] Response rate at the tumor assessment prior to surgery

The current application of neoadjuvant nivo+chemo followed by surgical resection and adjuvant treatment with nivolumab for subjects with resectable Stage II-IIIB NSCLC is based on the data from the pivotal Phase 3 Study CA20977T. The MAH did not seek Scientific Advice at CHMP regarding this clinical trial.

2.1.4. General comments on compliance with GLP, GCP

The clinical trials were performed in accordance with Good Clinical Practices (GCP) as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Nivolumab is a protein composed of natural amino acids. Proteins are expected to biodegrade in the environment and not be a significant risk. As a protein, nivolumab is exempt from preparation of an Environmental Risk Assessment under the 1 June 2006 "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/S/4447/00). Nivolumab and the product excipients do not pose a significant risk to the environment.

2.2.1. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

Nivolumab is human immunoglobulin G4 (IgG4) monoclonal antibody. Antibodies are considered naturally occurring proteins, which are not expected to remain either stable or biologically active in the environment for any significant period. The justification for not performing any ERA studies is accepted.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of nivolumab.

Considering the above data, nivolumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Type	Study Identifier; Report Location in CTD	Primary Study Objective	Study Design	Test Product(s); Dosage Regimen; Route of Administration	No. Subjects Treated	Study Population	Study Status; Type of Report
Efficacy Safety	Study Identifier: CA20977T (NCT04025879) Report location: Module 5.3.5.1	To compare EFS per BICR with nivo+chemo/ nivo vs placebo+chemo/ placebo	Phase 3, randomized, double-blind study of nivo+ chemo/nivo vs placebo+chemo/ placebo in subjects with resectable NSCLC	**Nivo+Chemo/Nivo Arm** Nivo 360 mg Q3W (IV) + SoC PDCT Q3W (IV) x 4 cycles as neoadjuvant treatment followed by surgery and post-surgical treatment with nivo 480 mg Q4W (IV) for up to 13 cycles (approximately 1 year) **Placebo+Chemo/Placebo Arm** Placebo Q3W (IV) + SoC PDCT Q3W (IV) x 4 cycles as neoadjuvant treatment followed by surgery and post-surgical treatment with placebo Q4W (IV) for up to 13 cycles (approximately 1 year) (placebo = normal saline or dextrose) For both treatment arms, selection of SoC PDCT was Investigator's choice, and dependent on NSCLC histology: SQ histology: • carboplatin (AUC 5 or AUC 6) + paclitaxel (175 mg/m^2 or 200 mg/m^2) • cisplatin (75 mg/m2) + docetaxel (75 mg/m^2) NSQ histology: • carboplatin (AUC 5 or AUC 6) + paclitaxel (175 mg/m2 or 200 mg/m^2) • carboplatin (AUC 5 or AUC 6) + pemetrexed 500 mg/m^2 • cisplatin 75 mg/m^2 + pemetrexed mg/m^2	Total: *458* Active arm: *228* Comparator arm: *230*	Subjects with Stage IIA (> 4 cm) to IIIB NSCLC (T3N2 or T4N2) per AJCC v8, with disease considered resectable	Study Status: Ongoing Type of Report: Final CSR

Abbreviations: AJCC: American Joint Committee on Cancer; AUC: area under the concentration-time curve; BICR: blinded independent central review; CSR: clinical study report; CTD: Common Technical Document; EFS: event-free survival; IV: intravenous; NSCLC: non-small cell lung cancer; NSQ: nonsquamous; PDCT: platinum-doublet chemotherapy; QxW: every x weeks; SoC: standard of care; SQ: squamous.

2.3.2. Bioanalytical methods

The validation method reports to quantify nivolumab and determine ADA and NAb in human serum were submitted from different laboratories: developed at USA or China. Nivolumab PK, ADA, and NAb samples from Study CA20977T sites in all countries except China were analysed in USA. PK, ADA, and NAb samples from sites in China were analysed in China.

Method validation for the quantification of nivolumab, ADAs and nAbs:

Developed and validated at USA:

Quantification of nivolumab (method MTD035):

For the quantification of nivolumab concentrations, method MTD0035 was validated at a provider located in the USA. The minimum required dilution was 1:100. Each calibration curve included 8 standards. Standard 0.1 µg/mL was used as anchor point.

Also, 100 µg/mL as dilution quality control was included for validation, dilution linearity and stability evaluation. Within-run and between-run accuracy and precision were within ±20% at the LLOQ and within ±15% at all other levels.

Ruggedness, robustness, selectivity (normal human sera and human cancer sera), haemolysis effect, ADA interference (up to 0.1 µg/mL), dilution linearity (up to 400-fold) and hook effect (not observed) were evaluated.

Lipemic effect was not evaluated.

Specificity was not evaluated as the effect of a concomitant medication on the quantification of nivolumab will be evaluated ad hoc for each study.

Stability was evaluated at different conditions. Freeze/Thaw cycle stability was demonstrated up to six cycles.

A cross-validation was carried out between two laboratories with QC samples at 4 different levels and 30 incurred sample pools. Results obtained were within ±15% for QC samples and within ±20% for at least 67% of the incurred sample pools.

Determination of ADAs (method MTD039):

For the detection, confirmation and titration of anti-nivolumab antibodies, method MTD039 was validated at a provider located in the USA .

Firstly, method MTD039 was validated using normal human serum. Later, an addendum was carried out to include method validation using disease human serum.

Original method validation report

Cut-points were determined for the screening (CPSC), confirmatory (CPC) and for the titer (CPT) assay in normal human serum samples. Intra-assay precision was within ±20% in screening, confirmatory and titer assays.

Selectivity was evaluated in 10 individual normal human serum samples and 25 individual disease state human serum samples (from which 5 were from NSCLC) spiked at the LPC and unspiked. Those samples were tested in screening and confirmatory assay and 3 out of the 5 samples unspiked were determined as potentially positive and then were confirmed as negative. All samples spiked at LPC were positive at screening and confirmatory. The MAH stated that this data indicates that different disease states may require separate CP evaluations.

No influence of haemolysis was observed up to and including 1100 mg/dL of haemoglobin. Lipaemic effect was not assessed. In addition, no hook effect was observed at concentrations up to and including 100 µg/mL of anti-BMS-936558 antibody.

From all the reports submitted, an addendum includes method validation using disease human serum to establish cut points in accordance with the population analysed.

Cut-points were determined for the screening (CPSC), confirmatory (CPC) and for the titer (CPT) assay in disease human serum samples.

Apart from CP determination, screening, confirmatory and titer sensitivity was also assessed. In the screening assay, the LPC concentration expected to produce a 1% plate failure rate was determined to be 5.02 ng/mL. No LPC concentration was evaluated for the titer assay.

Determination of NAbs (method 15400):

Method 15400 was employed to determine NAbs in human serum samples from the study CA20977T. Method 15400 is a cell-based assay, by Bristol-Myers Squibb Company.

Developed and validated in China:

Method 14BAS0310 was used to quantify nivolumab concentrations, method 14BAS0313 was used to determine ADAs and method 17BAS0389 was employed to determine NAbs in human serum samples from study CA20977T. They were developed at a provider located in China by Bristol-Myers Squibb Company.

Sample analysis for the quantification of nivolumab, ADAs and nAbs:

Analysed at USA laboratories:

Sample analysis - Quantification of nivolumab

The purpose of this study was to quantify nivolumab in human serum samples in support of clinical protocol CA20977T. According to the report, sample analysis is ongoing and additional data will be reported in a subsequent report.

Analyte concentrations were determined by interpolation from the standard curve in Watson LIMS using a four-parameter logistic (Marquardt) regression model with 1/Y weighting.

A total of 2943 PK samples were received in frozen conditions (except 4 samples, which were not analysed). The maximum time from sample collection to analysis was 894 days.

Out of those 2943 samples, nivolumab concentrations were quantified in 1424 samples (1510 samples correspond to placebo group and therefore, they were not analysed). Samples of patients in the nivolumab arm which were not analysed was due they were received at ambient temperature, misidentified samples, or samples not received at the bioanalytical lab.

Overall, 83 samples were reported as haemolysed and 3 samples as lipaemic.

A full calibration curve was provided in each run. The calibration curve consisted of 7 standard levels and one anchor point. For the accepted run, accuracy and precision were within ±25% at the LLOQ and ULOQ, and within ±20% at all other levels.

According to the MAH, two sets of QCs at each level were included in each analytical run, in duplicate wells, and one set of DQC (100 µg/mL) was also included when diluted samples were included in the run. For the accepted runs, at least 2/3 of QCs (LQS, MQC and HQC) and 50% at each concentration level were within ±20% of the nominal value at each concentration level.. Therefore, the samples that required dilutions on these runs, were re-analysed in different runs.

In total, 238 samples were reanalysed. Of those, 18 samples were inadvertent repeats. The rest of the samples were reanalysed due to result above limit of quantitation, result below limit of quantitation, unacceptable DQC or indeterminate replicates (above the limit of quantitation or below the limit of quantitation).

Incurred Sample Reanalysis (ISR) was performed on 148 samples. The %difference was within ±30% for at least 2/3 of the repeats.

Determination of ADAs :

Sample analyses were carried out at a provider located in the USA . A total of 2333 human serum samples were received (4 of them in ambient conditions). They were stored at -80ºC. The maximum time from collection to analysis was of 934 days.

The cut-points used for sample analysis were those established during method validation with cancer patient serum.

Each screening analysis batch included four replicates of negative control (NC) samples and two sets of positive control (PC) samples. Both the NC and PC samples and the patient’s samples were analysed for duplicate wells.

Out of the 2333 samples, 1543 samples were analysed (1102 samples dosed with nivolumab and 441 placebo samples).

Out of the 1102 samples analysed in the screening assay, 277 samples were positive and were further analysed in the confirmatory assay. Of them, 50 were confirmed positive and were further analysed in the titration assay.

Out of the 440 placebo samples analysed, 14 samples were confirmed positive.

Regarding the 790 samples that were not analysed: 776 were placebo samples, 5 samples were received in error, 4 samples were received in ambient conditions, 2 were duplicate samples, 2 were unassigned samples and one was collected in the wrong type of tube.

Determination of NAbs:

Forty-nine samples were received and were stored at -70ºC prior to analysis. The maximum time from collection to analysis was of 1053 days.

Out of the 49 samples analysed, only one sample was positive for neutralizing antibodies.

Analysed at the provider located in China:

Quantification of nivolumab:

The purpose of this study was to quantify nivolumab in human serum samples in support of clinical protocol CA20977T.

Analyte concentrations were determined by interpolation from the standard curve in Watson LIMS using a four-parameter logistic regression model with no weighting.

A total of 387 PK samples were received in frozen conditions. The maximum time from sample collection to analysis was 802 days.

Out of those 387 samples, nivolumab concentrations were quantified in 219 samples (168 samples correspond to placebo group and therefore, they were not analysed).

Samples were analysed in 15 runs (including ISR analysis), with a pass rate of 100%. The number of samples analysed per run was not provided.

A full calibration curve was provided in each run. The calibration curve consisted of 7 standard levels and one anchor point. For every run, accuracy and precision were within ±25% at the LLOQ and ULOQ, and within ±20% at all other levels.

According to the report, QCs at each level were included in each analytical run, in duplicate wells, except DQC level that was included in triplicate. For every run, at least 2/3 of QCs (LQS, MQC and HQC) and 50% at each concentration level were within ±20% of the nominal value at each concentration level. However, samples of the DQC were not within ±20% of the nominal value. Therefore, the samples that required dilutions on these runs, were re-analysed in different runs.

In total, 56 samples were reanalysed. The rest of the samples were reanalysed due to result above limit of quantitation, result below limit of quantitation or unacceptable DQC.

Incurred Sample Reanalysis (ISR) was performed on 21 samples. The %difference was within ±30% for at least 2/3 of the repeats.

Determination of ADAs:

A total of 289 human serum samples were received at the provider located in China. They were stored at -70ºC. The maximum time from collection to analysis was of 759 days.

The cut-points used for sample analysis were those established during method validation with cancer patient serum.

Each screening analysis batch included four replicates of negative control (NC) samples and two sets of positive control (PC) samples. Both the NC and PC samples and the patient's samples were analysed for duplicate wells.

Out of the 289 samples, 164 samples were analysed (125 samples correspond to placebo group and therefore, they were not analysed).

For the accepted runs, at least 2/3 of the QCs and 50% at each concentration level, the intra-assay precision was within ±20% between duplicates.

Out of the 164 samples analysed 3 samples were confirmed positive and were further analysed in the titration assay.

Determination of NAbs :

293 samples were at the provider located in China, and were stored at -70ºC prior to analysis. The maximum time from collection to analysis was of 898 days.

Three samples were analysed for NAbs. At least 2/3 of the QCs and 50% at each concentration level, the intra-assay precision was within ±30% between duplicates.

All three samples were negative for neutralizing antibodies.

2.3.3. Pharmacokinetics

CA20977T is a randomized, double-blind, Phase 3 study in subjects with resectable stage IIA-IIIB NSCLC. Subjects in Arm A (nivo+chemo/nivo) were randomized to receive neoadjuvant nivo+chemo, surgical resection, and adjuvant treatment with nivo. Subjects in Arm B (placebo+chemo/placebo) were randomized to receive neoadjuvant chemo, surgical resection, and adjuvant treatment with placebo

This study consisted of a Screening Phase, an On-treatment Phase consisting of the Neoadjuvant treatment and Adjuvant treatment (post-surgery), and a Post-discontinuation Follow-up Phase.

PK Objectives and endpoints

PK objectives and endpoints for study CA20977T are described in Table 2.

Objectives and endpoints

Table 2. Objectives and endpoints

Objective	Endpoint	Endpoint Description
Exploratory		
To characterize PK of nivo	PK measurements	Trough concentrations of nivolumab for PPK analyses, if warranted
To characterize the immunogenic potential of nivo	ADA	Frequency of nivolumab positive ADA. Samples collected from subjects were evaluated for ADAs and NAbs for nivolumab by validated methods. Immunogenicity status was defined as: **Baseline ADA Positive:** A subject with baseline ADA-positive sample. **ADA Positive:** A subject with ≥ 1 ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be ≥ 4-fold than baseline positive titer) after initiation of treatment: ***Persistent Positive*:** ADA-positive sample at 2 or more consecutive time points with the first and last ADA-positive samples at least 16 weeks apart. ***Not Persistent Positive-Last Sample Positive*:** Not persistent positive with a ADA-positive sample at the last sampling time point.

Objective	Endpoint	Endpoint Description
		Other Positive*:** Not persistent positive but some ADA-positive samples with the last sample being negative. ***Neutralizing Positive: At least 1 ADA-positive sample with neutralizing antibodies detected post-baseline. **ADA Negative**: No ADA-positive sample after the initiation of treatment.

Sampling times

PK and ADA samples were collected for all participants in both arms although only samples from patients in the nivolumab treatment arm were analysed.

All sampling times for nivolumab determination were collected pre-dose except for those planned after end of infusion on cycle 1, day 1 for both neoadjuvant and adjuvant treatment.

Serum samples for ADA analysis were collected pre-dose at eight different time points.

More information on the sampling schedule can be found in Table 3 below:

Table 3. Pharmacokinetic and ADA sampling schedule

Study Day of Sample Collection [a]	Event	Time Relative to nivolumab/placebo dose	Nivolumab PK Sample [b]	Nivolumab ADA Sample [b]
Neoadjuvant treatment (1 Cycle = 3 weeks)				
Cycle 1 Day 1	Predose [c]	0:00	X	X
	End of infusion [d]	0:30	X	
Cycle 2 Day 1	Predose [c]	0:00	X	X
Cycle 3 Day 1	Predose [c]	0:00	X	X
Adjuvant treatment (1 Cycle = 4 weeks)				
Cycle 1 Day 1	Predose [c]	0:00	X	X
	End of infusion [d]	0:30	X	
Cycle 2 Day 1	Predose [c]	0:00	X	X
Cycle 3 Day 1	Predose [c]	0:00	X	X
Cycle 7 Day 1	Predose [c]	0:00	X	X
Cycle 11 Day 1	Predose [c]	0:00	X	X

a Part A1 indicates 4 cycles of neoadjuvant treatment of nivolumab/nivolumab placebo + chemotherapy prior to surgery. Part A2 indicates adjuvant treatment of nivolumab/nivolumab placebo monotherapy post-surgery.

b If a subject discontinues nivolumab/nivolumab placebo treatment during the sampling period, PK and ADA samples should be only collected for the next 1 time point according to PK table.

c Predose samples should be collected just before the administration of nivolumab/nivolumab placebo (preferably within 30 minutes). If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected.

d EOI: End of Infusion. This sample should be taken immediately prior to stopping nivolumab/nivolumab placebo drug infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. EOI samples may not be collected from the same IV access as drug was administered.

Pharmacokinetic parameters

Nivolumab determination in PK samples was carried out for technology exploration purposes, and exploratory results were not reported. Therefore, no information on descriptive statistics was provided and no statistical analysis was conducted.

Pharmacokinetic and ADA results

During study CA20977T samples for nivolumab determination were collected, but exploratory results were not provided. The bioanalytical report 2304-15301 includes the results obtained in each sample analysed for each patient. No information on descriptive statistics was provided.

ADA results were provided in the primary clinical study report. ADA determination was carried out in those patients who received nivolumab therapy. Of those, 198 were ADA evaluable subjects. Before initiating nivolumab treatment, 10 (5.1%) patients were nivolumab ADA positive. After start of treatment, 24 (12.1%) subjects were nivolumab ADA positive. The highest titer value observed in nivolumab ADA positive subjects was 128, which occurred in 2 subjects. Of the 198 nivolumab ADA evaluable subjects, 1 (0.5%) was neutralizing ADA positive.

ADA analysis is summarized in Table 4, which includes all nivo+chemo/nivolumab treated subjects with at least one post-baseline assessment in the global population.

Table 4. ADA assessments summary

	Arm A: Nivo + Chemo / Nivo
Subject ADA Status (%)	Nivolumab ADA N = 198
BASELINE ADA POSITIVE	10 (5.1)
ADA POSITIVE	24 (12.1)
PERSISTENT POSITIVE (PP)	1 (0.5)
NOT PP - LAST SAMPLE POSITIVE	3 (1.5)
OTHER POSITIVE	20 (10.1)
NEUTRALIZING POSITIVE	1 (0.5)
ADA NEGATIVE	174 (87.9)

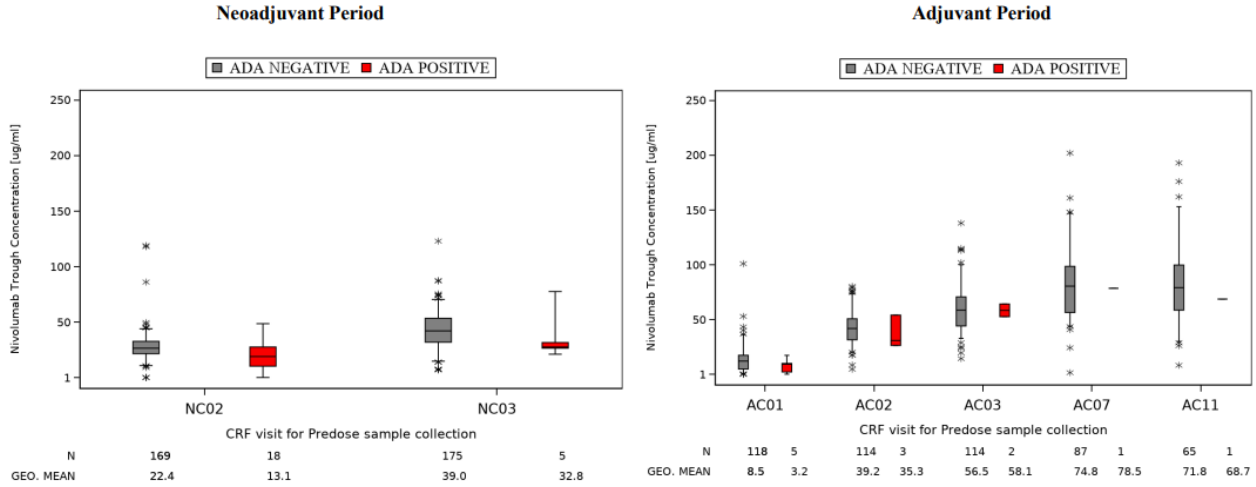
Baseline ADA Positive: A subject with baseline ADA-positive sample.
ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater than baseline positive titer) at any time after initiation of treatment
- **Persistent Positive (PP):** ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA positive samples are at least 16 weeks apart
- **Not PP-Last Sample Positive:** Not persistent but with ADA-positive sample at the last sampling timepoint
- **Other Positive:** Not persistent but some ADA-positive samples with the last sample being negative
- **Neutralizing Positive:** At least one ADA-positive sample with neutralizing antibodies detected post-baseline

ADA Negative: A subject with no ADA-positive sample after initiation of treatment. Post-baseline assessments are assessments reported after initiation of treatment.

The effect of immunogenicity on pharmacokinetics was assessed. Figure 1 presents the distribution of nivolumab trough concentrations over time by ADA status (negative or positive).

Overall, distributions of observed trough concentrations were similar between ADA positive and ADA negative subjects and most ADA positivity occurred early during the neoadjuvant and adjuvant periods.

Figure 1. Distribution of trough concentrations at each assessment over time by ADA status



AC -adjuvant cycle **NC** - neoadjuvant cycle

Each box represents the median, 25th, and 75th percentile of trough concentration distribution.

The whiskers represent 5th and 95th percentile of the distribution. The stars indicate outliers.

Dose selection and rationale/justification

The proposed dosing regimen of nivolumab 360 mg + platinum-doublet chemotherapy Q3W for up to 4 cycles as neoadjuvant treatment followed by post-surgical nivolumab 480 mg Q4W as adjuvant treatment for up to 13 cycles (up to 1 year) in patients with resectable stage IIA-IIIB NSCLC evaluated in CA20977T was based on extensive characterization of nivolumab PK and E-R across various tumour types, including previously conducted PopPK28 and E--R29 analyses in resectable early-stage NSCLC.

A nivolumab 360 mg Q3W (for up to 4 cycles) dosing regimen was selected for neoadjuvant treatment in CA20977T as it allowed synchronization with the four 3-week cycles of the coadministered chemotherapy and is consistent with clinical practice. The use of 4 cycles of neoadjuvant nivolumab + chemotherapy treatment in CA20977T was consistent with the standard chemotherapy regimen as per the NCCN guidelines at the time of study initiation. Notably, nivolumab 360 mg Q3W in combination with platinum-based chemotherapy is now approved for neoadjuvant treatment of early-stage resectable NSCLC, supporting the selection of this dose for neoadjuvant treatment in Study CA20977T.

Selection of nivolumab 480 mg Q4W monotherapy for adjuvant treatment offered the most convenient (least frequent) dosing option to subjects in Study CA20977T. The adjuvant dose selection was also based on clinical data and modelling and simulations of nivolumab weight-based and flat dosing regimens across multiple tumour types and lines of treatment showing that the benefit-risk profiles of nivolumab 480 mg Q4W are comparable to 3 mg/kg Q2W.

2.3.4. Discussion on clinical pharmacology

No new clinical pharmacology data were submitted in the current application, which is acceptable since the clinical pharmacology profile of nivolumab has been characterised in several tumour types, including NSCLC, with and without concomitant chemotherapy. However, PK and immunogenicity

exploratory endpoints were included in study CA20977T, therefore analytical methods and PK and ADA results have been assessed.

Analytical methods

Validation reports from different laboratories located in the USA and in China were submitted. The applied methods in China laboratory (method 14BAS0310, method 14BAS0313 and method 17BAS0389) and method 15400 to determine NAbs at USA laboratory were evaluated in previous procedures and considered acceptable. Methods used at USA to quantify nivolumab in human serum (MTD035) and to determine ADAs (MTD039) have been assessed in this procedure.

Cross validation between analytical methods to quantify nivolumab concentrations and to determine anti-nivolumab antibodies were provided. The MAH provided a cross-comparison between both methods to determine NAbs. However, this cross-comparison was not considered acceptable. Cross-comparison cannot be assumed as negative samples used did not meet the acceptance criteria. Additionally, samples used during this assessment were not from patients, as they were created from normal human serum. Considering that samples yielding negative results at the laboratory located in China were also negative at BMS laboratory, the issue was no longer pursued. However, the MAH is advised that a new cross-comparison between both methods is necessary in the future. This cross-comparison should consider the possible matrix effect due to differences in human serum and should be performed using patient sera.

Overall, the validation of method MTD035 to quantify nivolumab in human serum at the USA provider was carried out successfully. Accuracy and precision of VS were determined following the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

The MAH disregarded one run, however this run should have not been rejected according to the EMA Guideline on bioanalytical method validation. For future procedures, the MAH should follow the Guideline criteria for run rejection. Results on ruggedness, robustness, impact of ADA, stability, selectivity (normal human sera, human cancer sera and haemolysed sera) and cross-validation were provided and are acceptable. Specificity was not evaluated and the report indicates that it will be evaluated ad hoc for each study. This should be taken into account for each study in which this method is used.

No information on lipemic effect during method validation was provided. Considering the MAH statement that MTD035 is the exact same method as ICD416 and 14BASM122; that no lipemic effect was shown in those methods, and that removing the only lipemic sample included in the immunogenicity analysis will have no impact on the interpretation of results, this issue is not further pursued. For future procedures, the MAH is encouraged to perform a validation of lipemic effect in line with ICH M10 Guideline on method MTD035.

Overall, within-run and between-run accuracy and precision were within ±20% at the LLOQ and within ±15% at all other levels. Nevertheless, according to the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**), accuracy and precision should be evaluated at a minimum of 4 concentration levels: "the LLOQ, within three times the LLOQ (low QC), around 30 - 50% of the calibration curve range (medium QC), and at least at 75% of the upper calibration curve range (high QC)". For future procedures, the MAH should include the low QC, medium QC and high QC that comply with the ICH M10 Guideline.

Dilution linearity and hook effect was assessed. Overall, the results were acceptable although the accuracy obtained at the last dilution factor (400-fold) was -20.7%. The MAH should take into account that dilutions up to 400-fold are not recommended during sample analysis.

Method MTD039 to determine anti-nivolumab antibodies was validated. Studies to evaluate and determine precision, sensitivity, drug tolerance, hook effect, selectivity, haemolysis effect and short-term stability were carried out. They are considered acceptable.

Although sensitivity assay was performed using normal human serum, LPC determination was not carried out. It is important to carry out LPC determination during sensitivity analysis to ensure consistent assay performance at CP levels. These LPCs should be calculated to a 1% failure rate. The issue was not further pursued, however, the MAH should consider it for future procedures.

Selectivity results in normal human sera and for samples spiked with haemoglobin were acceptable. However, no information on lipaemic effect was provided and according to the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**), the sources used to evaluate selectivity should include lipaemic samples. Lipemia can influence sample analysis whether in a physical, chemical, non-homogeneity and spectrophotometric manner. Lipemia can interfere with antigen-antibody reaction. The methods preferred to remove lipemia from a sample are centrifugation or extraction. For future procedures, the MAH is encouraged to perform a validation of lipemic effect in line with ICH M10 Guideline on method MTD039.

After cut-point (CP) determination in disease human serum samples, assay sensitivity and LPC concentration expected to produce a 1% plate failure rate was determined for screening assay. However, the LPC used (50 ng/mL) during method validation was not in accordance with the LPC calculated (5.02 ng/mL). This is not in accordance with the actual state of the art as choosing a LPC with an unreasonably high concentration may produce an assay signal that is substantially above the cut point. For future procedures, the MAH should consider adjusting the LPC concentration used based on the LPC calculated expected to produce a 1% plate failure rate.

Sample analysis

Overall, sample analysis to quantify nivolumab in human serum was carried out in accordance with method validation and ICH M10 Guideline on bioanalytical method validation and study sample analysis. Some issues arose during the assessment but all of them were address. Of note, during sample analysis at USA laboratories several samples were reanalysed due to different reasons. For future procedures the MAH should only consider the initial concentrations unless otherwise justified.

PK and ADA results

Both PK and ADA analysis were exploratory objectives. Although PK samples were obtained to measure nivolumab concentrations, exploratory results were not provided neither descriptive statistics.

On the other hand, anti-nivolumab antibodies were analysed during treatment and post-treatment to evaluate the existence of ADA during CA20977T study in patients included in arm A (nivo+chemo/nivo). This is in accordance with the Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1).

At baseline, 5.1% of the patients were ADA positive and during treatment, 12.1%. According to the results, trough concentrations were similar between ADA positive and ADA negative subjects and only one patient was positive for neutralizing antibodies.

2.3.5. Conclusions on clinical pharmacology

Both PK and ADA analysis were exploratory objectives. Overall, the analytical methods evaluated (those developed at USA) and sample analysis were in line with the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-response study was submitted as part of this application.

2.4.2. Main study

Study CA20977T - A Phase 3, Randomized, Double-blind Study of Neoadjuvant Chemotherapy plus Nivolumab versus Neoadjuvant Chemotherapy plus Placebo, followed by Surgical Resection and Adjuvant Treatment with Nivolumab or Placebo for Participants with Resectable Stage II-IIIB Non-Small Cell Lung Cancer (NSCLC)

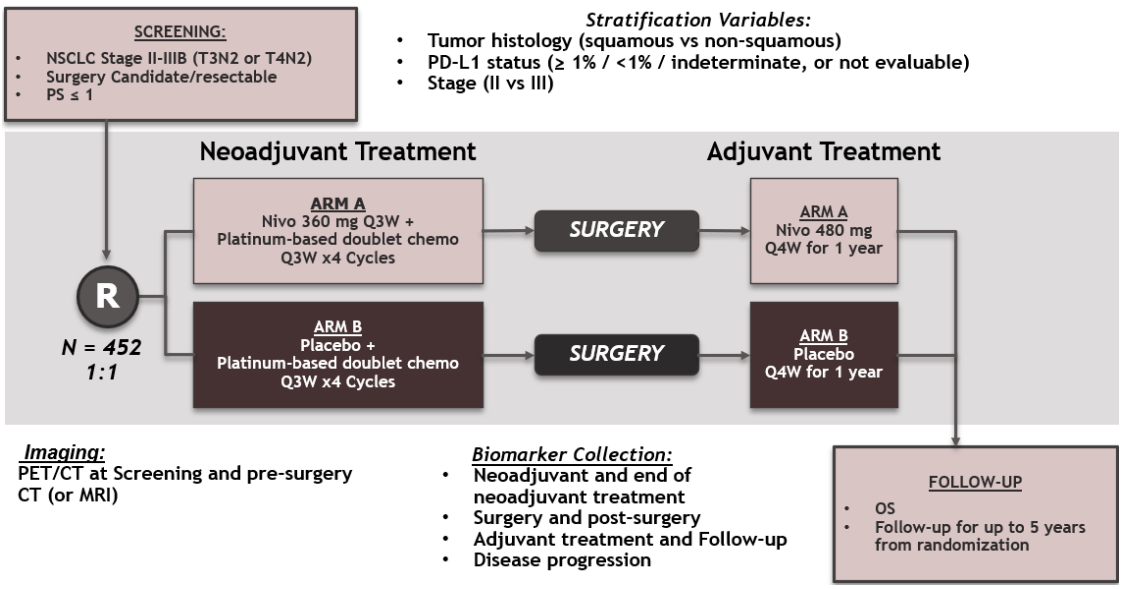
Methods

Study CA20977T is a randomized, double-blind, Phase 3 study in subjects with resectable early-stage NSCLC: Stage IIA (> 4 cm) to IIIB (T3N2 or T4N2). Subjects with N3 nodal disease were not eligible. Subjects with resectable T4 tumour size with Stage IIIA or IIIB disease could have been reviewed and approved for participation in the study by the multidisciplinary team (including surgeon, medical oncologist, and radiation oncologist).

The global study population includes all subjects enrolled during the global accrual window. Any subjects from China enrolled during the global accrual window were included in the global study population.

A China substudy was added per a country specific protocol amendment. There are 68 subjects who were treated at Chinese sites and are included in the China substudy: 47 of the 68 subjects from China are included in both the global population and the China substudy and 21 of the 68 subjects are included in the China substudy only. Results from subjects in the China substudy are not in scope for this submission.

Figure 2. CA20977T Study Design Schematic



Study participants

Main inclusion criteria

- *Type of participant and target disease characteristics*

a) Participants with suspected or histologically confirmed **Stage IIA** (> 4 cm) **to IIIB** (T3N2) NSCLC (per the American Joint Committee on Cancer (AJCC) Cancer Staging Manual 8th Edition) with disease that is considered resectable.

   Note: Participants must be evaluated by the multidisciplinary team (including surgeon, medical oncologist, radiation oncologist, etc) during screening.

   Note: Participants with N3 nodal disease are not eligible. Participants with resectable T4 tumour size with Stage IIIA or IIIB disease must be reviewed and approved for participation in the study by the multidisciplinary team (including surgeon, medical oncologist, radiation oncologist, etc). The review of the multidisciplinary team must be documented in CRF and medical record.

b) No brain metastasis.

c) Participant must be deemed eligible for complete resection and must agree to undergo standard of care surgery for complete resection of NSCLC after neoadjuvant therapy

d) Treatment-naive for NSCLC (no prior systemic anti-cancer treatment)

e) Ability to provide surgical or biopsy tumour tissue for biomarkers (e.g., whole exome sequencing, PD-L1 testing, etc.).

   i. All participants must have tissue submitted to a central laboratory during screening. Either formalin-fixed paraffin embedded (FFPE) (preferred) tissue block or 5-10 unstained tumour tissue slides, obtained within 3 months prior to enrolment, with an associated pathology report, must be submitted to the central laboratory for inclusion. Biopsy should be excisional, core needle, or surgical specimen. Fine needle aspiration is unacceptable for submission. The central laboratory must provide IRT with PD-L1 status prior to randomization.

f) Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1

Main exclusion criteria

- *Medical Conditions*

a) Participants with EGFR mutation regardless of mutation type are excluded. Non-squamous tumours with unknown EGFR mutation status must be tested for EGFR mutation. Use of a FDA-approved or local Health Authority-approved test (tissue or blood) is strongly encouraged.

b) Participants with known ALK mutations.

c) Participants with Grade ≥ 2 peripheral neuropathy.

d) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol.

e) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

f) Participants with interstitial lung disease or active, non-infectious pneumonitis (symptomatic and/or requiring treatment) that may interfere with the detection or management of suspected drug-related pulmonary toxicity.

g) Participants with previous malignancies (except non-melanoma skin cancers, and in situ cancers such as the following: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to first treatment and no additional therapy is required or anticipated to be required during the study period.

h) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

i) Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.

j) Participants with serious or uncontrolled medical disorders.

- *Prior/Concomitant Therapy*

a) Any previous anti-cancer treatment including cytotoxic, IO treatment, targeted agents, or radiotherapy for NSCLC

b) Treatment with botanical preparations (e.g., herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally.

c) Participants who have received a live/attenuated vaccine within 30 days of randomization

d) Prior treatment with any anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

Treatments

Treatments administered

Table 5. Selection and Timing of Dose

Study Treatment	Unit dose strength/ Dosage level	Dosage formulation Frequency of Administration	Route of Admin.
BMS-936558 Nivo[a]	10 mg/mL	360 mg on Day 1 of a 3-week cycle for up to 4 cycles as neoadjuvant therapy 480 mg on Day 1 of a 4-week cycle for up to 13 cycles (approximately 1 year) as adjuvant therapy	IV
Carboplatin	10 mg/mL	AUC 5 or AUC 6 on Day 1 of a 3-week cycle for up to 4 cycles[a,b]	IV
Cisplatin	1 mg/mL	75 mg/m^2 on Day 1 of a 3-week cycle for up to 4 cycles[a]	IV
Docetaxel	10 mg/mL	75 mg/m^2 on Day 1 of a 3-week cycle for up to 4 cycles[a]	IV
Paclitaxel (Taxol)	6 mg/mL	175 mg/m^2 or 200 mg/m^2 on Day 1 of a 3-week cycle for up to 4 cycles[a]	IV

Study Treatment	Unit dose strength/ Dosage level	Dosage formulation Frequency of Administration	Route of Admin.
Pemetrexed	500 mg/vial	500 mg/m^2 on Day 1 of a 3-week cycle for up to 4 cycles[a]	IV

[a] Subjects in the placebo+chemo/placebo arm received normal saline or dextrose following the same dosing schedule as that for nivo.

[b] Carboplatin is initiated at a dose of AUC 5 or 6.

Histology-based chemotherapy:

- Squamous histology:
  - carboplatin (AUC 5 or AUC 6) + paclitaxel (175 mg/m^2 or 200 mg/m^2)
  - cisplatin (75 mg/m^2) + docetaxel (75 mg/m^2)
- Non-squamous histology:
  - carboplatin (AUC 5 or AUC 6) + pemetrexed (500 mg/m^2)
  - cisplatin (75 mg/m^2) + pemetrexed (500 mg/m^2)
  - carboplatin (AUC 5 or AUC 6) + paclitaxel (175 mg/m^2 or 200 mg/m^2)

Neoadjuvant treatment

Neoadjuvant treatment (nivo+chemo or placebo+chemo) was given until disease progression, unacceptable toxicity or completion of 4 cycles, whichever came first. Subjects were to be dosed no less than 18 days from the previous dose during Q3W cycles.

No dose escalations or reductions of nivolumab were allowed; however, dose delays were permitted for laboratory abnormalities or AEs. Dose reductions and dose delays of chemo for hematologic toxicities and/or AEs were allowed.

Following the completion of neoadjuvant treatment, all subjects who remained operative candidates underwent definitive surgery for NSCLC within 6 weeks.

Adjuvant treatment

Subjects were to complete 13 cycles (approximately 1 year) of adjuvant treatment except in the event of disease progression, disease recurrence, death, unacceptable toxicity, symptomatic deterioration, investigator's decision to discontinue treatment, the subject's decision to discontinue treatment or withdraw consent, the subject being lost to follow-up, end of the study, or BMS decision to terminate the study.

Objectives

Table 6. Objectives and Endpoints – CA20977T Global Population

Objective	Endpoint	Endpoint Description
Primary		
To compare EFS (by BICR) in Arm A vs Arm B	EFS by BICR	EFS (by BICR per RECIST 1.1): time from randomization to any event of progression of disease or worsening of disease precluding surgery, if surgery was attempted but gross resection was abandoned due to unresectable tumour or worsening of disease, progression or recurrence of disease after surgery, progression or recurrence of disease without surgery, or death due to any cause.
Secondary		
To compare OS in Arm A vs Arm B	OS	OS: time between the date of randomization and the date of death due to any cause. OS was censored on the last date a subject was known to be alive.
To assess pCR rate (by BIPR) in Arm A vs Arm B	pCR rate by BIPR	pCR rate: the number of randomized subjects with absence of residual viable tumour in lung and lymph nodes as evaluated by BIPR, divided by the number of randomized subjects for each arm.
To assess MPR rate (by BIPR) in Arm A vs Arm B	MPR rate by BIPR	MPR rate: the number of randomized subjects with ≤ 10% residual viable tumour in lung and lymph nodes as evaluated by BIPR, divided by the number of randomized subjects for each arm.
To assess safety and tolerability in Arm A vs Arm B	Safety	Frequency of deaths, AEs, SAEs, select AEs, IMAEs, OESIs, and laboratory abnormalities. AEs were coded using MedDRA version 26.0. AEs and laboratory values were graded for severity using NCI CTCAE version 4.0.
Exploratory		
To assess ORR by BICR in Arm A vs Arm B	ORR by BICR	ORR: the proportion of randomized subjects with an overall radiological response prior to definitive surgery (no confirmation required) of CR or PR by BICR using RECIST 1.1 criteria. If no surgery, the first scheduled tumour assessment per protocol was used to assess ORR. Subjects who received alternative anti-cancer therapy before presurgery tumour assessment were counted as non-responders.
To assess TTDM per investigator in Arm A vs Arm B	TTDM by investigator	TTDM: the time between date of randomization and the first date of distant metastasis or date of death in the absence of distant metastasis. Distant metastasis: any new lesion outside of the thorax or in the contralateral lung using RECIST 1.1 (per investigator). Subjects who had not developed distant metastasis or died at the time of analysis were censored on the date of their last evaluable tumour assessment.
To assess EFS by BICR, MPR rate and pCR rate by PD-L1 status in Arm A vs Arm B	EFS, MPR rate and pCR rate by PD-L1	Relation of baseline expression levels of tumour cell PD-L1 with EFS, MPR, and pCR Tumour cell PD-L1 expression was defined as the percent of tumour cells with membrane staining in a minimum of 100 evaluable tumour cells per validated Agilent/Dako PD-L1 IHC 28-8 pharmDx test. Tumour cell PD-L1 status was: ≥ 1% (≥ 1% of tumour cells with membrane staining in a minimum of 100 evaluable tumour cells), < 1% (<

Objective	Endpoint	Endpoint Description
		1% of tumour cells with membrane staining in a minimum of 100 evaluable tumour cells), or PD-L1 not quantifiable (including indeterminate, not evaluable or missing).
To assess the feasibility of surgery and rate of peri- and post operative complications (within 90 days of surgery) in Arm A vs Arm B	Feasibility of surgery, rate of peri- and post- operative complications	Proportion of subjects with delayed or cancelled surgery, duration of surgery, length of hospital stay, surgical approach, incidence of AEs/SAEs associated with surgery including intraoperative complications (e.g., pneumonitis, ARDS, PRBC, bronchopleural fistulas, air leaks, etc), re-admission to the Intensive Care Unit, atrial fibrillation. other supraventricular tachycardia (SVT), etc to 90 days post-surgery
To assess changes in health status and HRQoL	EQ-5D-3L VAS & UI scores	Mean change from baseline, time to deterioration, and the proportion of subjects without meaningful deterioration in EQ-5D-3L VAS and UI. See Section 9.1.4 of the protocol (Appendix 16.1.1). The EQ-5D-3L [1,i] (standardized instrument used to measure health status and functioning) has 2 components: descriptive system and VAS. The descriptive system has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels reflecting "no (level 1)," "moderate (level 2)," and "extreme health problems (level 3)." A VAS allows respondents to rate their own current health on a 100-point scale ranging from 0 = "worst imaginable" health to 100 = "best imaginable" health state.
To assess changes in physical function	PROMIS T-scores	Mean change from baseline in PROMIS T-score based on the PROMIS PF 8c. See Section 9.1.4 of the protocol (Appendix 16.1.1). The PROMIS contains a subset of 8 items selected (for their relevance to cancer patients) from the PROMIS Physical Function item bank. Each item assesses the difficulty in performing different activities using a 5-level verbal rating scale.
To assess changes in disease-related symptoms and impacts on HRQoL in Arm A vs Arm B	FACT-L and NSCLC-SAQ scores	Time to symptom deterioration, proportion of subjects without meaningful symptom deterioration for NSCLC-SAQ and the LCS subscale of the FACT-L. Mean change from baseline in FACT-L total and subscale scores and NSCLC-SAQ total score. FACT-L (widely used, reliable, and valid measure) has 36-items to measure multi-dimensional QoL using a 5-point Likert scale. FACT-L, version 4, is a combination of the 27-item FACT-G and 9-item LCS. A subset of 7 items (2/9 items were not administered) from the LCS was used to calculate the FACT LCS (assess disease-specific symptom severity). NSCLC-SAQ (7-items) measures overall severity of the NSCLC symptoms (cough, pain, dyspnoea, fatigue, and appetite). A total FACT-G score is calculated by summing the PWB, SWB, EWB, and FWB subscale scores. A total FACT-L score is obtained by summing the FACT-G score with LCS, thus adding lung cancer–specific QoL information to the FACT-G. Each item was scored on a 5-point scale from 0 (Not at all) to 4 (Very much). Higher scores indicate greater HRQoL.

Objective	Endpoint	Endpoint Description
To characterize subject perceptions of the bothersomeness of symptomatic AEs	GP5 scores from the FACT-L	GP5 item from the FACT-L. The GP5 item from the FACT-G is used to assess the bother associated with the side effects of treatment. It was scored on a 5-point scale from 0 (Not at all) to 4 (Very much). Higher scores indicate greater HRQoL.
Assess measurement properties of NSCLC-SAQ	NSCLC-SAQ scores	Reliability, validity, and responsiveness of the NSCLC-SAQ. See the description above.
To characterize PK of nivo	PK measurements	Trough concentrations of nivolumab for PPK analyses, if warranted
To evaluate the efficacy after next line of treatment	EFS2 per investigator[a]	EFS2: time from randomization to disease progression on next line of treatment (per investigator assessment), or death from any cause, whichever occurred first. If EFS2 could not be reliably determined, the start date of the next-line treatment was used. A subject who neither progressed after next line of treatment nor died was to be censored on the date of his/her last known alive date.
To characterize the immunogenic potential of nivo	ADA	Frequency of nivolumab positive ADA. Samples collected from subjects were evaluated for ADAs and NAbs for nivolumab by validated methods. Immunogenicity status was defined as: **Baseline ADA Positive:** A subject with baseline ADA-positive sample. **ADA Positive:** A subject with ≥ 1 ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be ≥ 4-fold than baseline positive titer) after initiation of treatment: ***Persistent Positive*:** ADA-positive sample at 2 or more consecutive time points with the first and last ADA-positive samples at least 16 weeks apart. ***Not Persistent Positive-Last Sample Positive*:** Not persistent positive with a ADA-positive sample at the last sampling time point. ***Other Positive*:** Not persistent positive but some ADA-positive samples with the last sample being negative. ***Neutralizing Positive:*** At least 1 ADA-positive sample with neutralizing antibodies detected post-baseline. **ADA Negative**: No ADA-positive sample after the initiation of treatment.
To evaluate biomarkers in tumour and peripheral blood as potential predictive biomarkers of efficacy	Biomarkers and their association with efficacy	Gene expression signatures (e.g. tumour inflammation, immune cell infiltration etc), driver mutations (e.g. STK11, KRAS) as well as peripheral markers and soluble factors within blood (e.g., cytokines, solHLA) and other factors within blood (e.g., MDSC) and their association with clinical outcomes (EFS, pCR, mMPR, cRR) Circulating tumour DNA for blood TMB and/or MRD analysis.

[a] EFS2 is called PFS2 in the protocol.

Arm A: nivolumab 360 mg Q3W + SOC platinum-based doublet chemo Q3W x 4 cycles as neoadjuvant treatment followed by surgery and post-surgical treatment with nivolumab 480 mg Q4W for up to 13 cycles (approximately 1 year)

Arm B: placebo Q3W + SOC platinum-based doublet chemo Q3W x 4 cycles as neoadjuvant treatment followed by surgery and post-surgical treatment with placebo Q4W for up to 13 cycles (approximately 1 year)

Global study population: includes all subjects enrolled during the global accrual window. Any subjects from China enrolled during the global accrual window were included.

Sample size

In this study, the sample size was calculated to compare EFS between Arm A and Arm B under a two-side 0.05 type I error with 90% power consideration. The number of events was estimated assuming an exponential distribution for EFS in each arm.

Approximately 452 randomized subjects were planned to be randomised to the two treatment arms. Approximately 231 EFS events would provide 90% power to detect a EFS HR of 0.65 with a type 1 error of 0.05 (2-sided). A HR of 0.65 corresponds to a 54% increase in the median EFS, assuming a median EFS of 21.0 months for Arm B (placebo+chemo/placebo) and 32.3 for Arm A (nivo+chemo/nivo).

An interim analysis was planned after 185 EFS events (80% information fraction) had occurred. The final analysis is planned after 231 EFS events have occurred. The stopping boundaries at the interim and final analyses were based on the actual number of EFS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the interim analysis was performed exactly at 185 events, the study could be stopped by the DMC for EFS superiority if the p-value is ≤0.025.

If the superiority of EFS per BICR assessment for the comparison between treatment groups is demonstrated at a two-sided type I error rate 0.05, OS was to be tested hierarchically.

Approximately 174 events, among the 452 subjects randomized to Arms A and B provides 80% power to detect a hazard ratio of 0.65 with a type I error of 0.05. The HR of 0.65 corresponds to a 54% increase in the median OS, assuming a median OS of 40 months for Arm B and 61.5 months for Arm A. One interim analysis was planned at the time of the EFS FA (where 80% of the total number of events are projected to have occurred around 140 events). The stopping boundaries at the interim and final analyses will be based on the actual number of OS events at the time of the analysis using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. If the first interim analysis was performed exactly at 140 events, a p-value ≤ 0.025 would result in a statistically significant improvement in OS. The nominal significance level for the final look of OS after 174 events would then be 0.043.

Randomisation

Eligible subjects were randomized 1:1 using an IRT system. The randomization was based on randomization lists generated using permutated blocks and stratified by tumour histology (SQ vs NSQ), NSCLC stage (II vs III), and PD-L1 status (≥ 1% vs < 1% vs indeterminate/not evaluable).

Blinding (masking)

The study was conducted as a double-blind study. The Sponsor, subjects, investigator, and site staff were blinded to the study therapy administered prior to the clinical data cut-off (26-Jul-2023) with the following exceptions:

- Treatment allocation (nivolumab vs placebo) was only available through the IRT to an unblended pharmacist or other individuals who were responsible for dispensing blinded study drug. These individuals were unblinded to study drug identification but were not involved in any other aspect of study conduct.

- Designated staff and associates of the Sponsor could have been unblinded to the treatment assignment of an individual subject for the following reasons: emergency safety reasons, SUSAR reporting, pregnancy, progression, and received subsequent therapy.
- Designated staff in the BMS Bioanalytical Sciences department (and/or a designee in the external bioanalytical laboratory) could have received the randomization treatment assignments in order to minimize unnecessary bioanalytical analysis of PK and immunogenicity samples.

A list of the subjects who were unblinded prior to database lock for emergency safety reasons has been provided.

Statistical methods

Populations for analyses

- Global study population: all subjects enrolled during the global accrual window (from first patient first consent date to last patient outside of China's consent date). Any patients from China enrolled during the global accrual window will be included.
- All Enrolled Subjects: All participants who signed an informed consent form and were registered into the IRT during the global enrolment period.
- All Randomized Subjects: All participants from the global study population who were randomized to any treatment group in the study. This population will be used for analyses of study conduct and study population. Analysis of demography, protocol deviations, baseline characteristics, COAs and efficacy will be performed for this population.
- All Treated Subjects: All participants from the global study population who received at least one dose of any study medication in neoadjuvant or adjuvant setting. This is the primary dataset for drug exposure and safety analysis.
- All Adjuvant Therapy Treated Subjects: All participants from the global study population who received at least one dose of adjuvant therapy medication. This is the primary dataset for adjuvant therapy drug exposure and safety analysis.
- PK Subjects: All participants from the global study population treated with nivolumab with available serum time-concentration data.
- Immunogenicity (ADA evaluable) Subjects: as all treated subjects from the global study population with baseline and at least 1 post-baseline pre-infusion/administration evaluable (i.e., positive, negative) immunogenicity assessment.

Event-Free Survival (Primary Analysis)

The primary definition of EFS, censoring for subsequent anticancer therapy, was used for the primary analysis of EFS. At the interim analysis, EFS for nivo+chemo/nivolumab vs placebo+chemo/placebo was compared using a stratified log-rank test, with stratification factors per IRT; a 2-sided p-value was reported. A Lan DeMets α-spending function with O'Brien and Fleming type of boundary was employed to determine the nominal significance level. The HR and the corresponding (1-adjusted alpha) CI were estimated for nivo+chemo/nivolumab vs placebo+chemo/chemo using a stratified Cox proportional hazards model with the randomized arm as a single covariate.

EFS was estimated using KM techniques and was displayed graphically. A 2-sided 95% CI for median EFS in each arm was computed via the log-log transformation method. EFS rates at fixed time points were presented along with their associated 95% CIs.

At this first planned EFS interim analysis, 189 EFS events (81.8% information fraction) were recorded in the database. The alpha boundary (Lan DeMets α spending function with O'Brien and Fleming type of boundary) for this interim analysis was 0.0264. Since the EFS comparison was statistically significant at the EFS interim analysis, the EFS analysis after observing 231 events would be descriptive (only the point estimate and 95% CI will be presented).

A formal interim analysis for OS (secondary endpoint) was not planned at the time of the EFS interim analysis. Per the SAP, the formal OS interim analysis was planned when approximately 140 OS events have occurred. The OS final analysis is planned after approximately 174 events are observed.

Table 7. Attributes of the Main Estimand for Primary Objective (EFS per BICR) Primary Definition

Attribute	Definition Details		
Treatment	Nivo+chemo neoadjuvant followed by surgery and nivolumab adjuvant vs placebo+chemo neoadjuvant followed by surgery and placebo adjuvant		
Population	Subjects with resectable early stage (Stage IIA [> 4 cm] to IIIB [T3N2 or T4N2]) NSCLC		
Variable	EFS: the length of time from randomization to any of the following events: progression of disease or worsening of disease precluding surgery, if surgery was attempted but gross resection was abandoned due to unresectable tumour or worsening of disease, progression, or recurrence of disease after surgery, progression or recurrence of disease without surgery, or death due to any cause. Progression/recurrence assessed by BICR per RECIST 1.1.		
Intercurrent Events	**Event**	**Strategy**	**Description**
	Discontinuation of study therapy	Treatment Policy Strategy	Progression, recurrence, or death that occurred after discontinuation of study therapy was counted
	Subsequent anti-cancer therapy prior to events	While on treatment Strategy	Observations after subsequent anticancer therapy were excluded/censored. EFS censored on the date of last evaluable tumour assessment or surgery conducted prior to or on the date of initiation of subsequent anticancer therapy.
	Surgery cancelled or abandoned due to other than progression disease, worsening disease or tumour not resectable	Treatment Policy Strategy	Progression or death that occurred post-planned surgery were counted
	Secondary primary cancer	While on treatment Strategy	Observations that occurred post-secondary primary cancer were excluded/censored. EFS censored on the date of the last evaluable tumour assessment or surgery conducted prior or on the date of secondary primary cancer identified by BICR
Population-level Summary	HR estimated by stratified Cox proportional hazard model		

Table 8. Summary of Attributes of the Supplemental Estimand for Primary Objective-EFS Secondary Definition

Attribute	Definition Details		
Treatment	Nivo+Chemo neoadjuvant followed by surgery and Nivolumab adjuvant vs. Placebo+Chemo neoadjuvant followed by surgery and placebo adjuvant		
Population	Patients with Resectable early stage (Stage IIA [> 4 cm] to IIIB [T3N2 or T4N2]) NSCLC		
Variable	EFS is defined as the length of time from randomization to any of the following events: progression of disease or worsening of disease precluding surgery, if surgery is attempted but gross resection is abandoned due to unresectable tumour or worsening of disease, progression or recurrence of disease after surgery, progression or recurrence of disease without surgery, or death due to any cause. Progression/recurrence will be assessed by BICR per RECIST 1.1.		
Intercurrent Events (ICEs)	**Event**	**Strategy**	**Description**
	Discontinuation of study therapy	Treatment Policy Strategy	Progression, Recurrence or death that occurs after discontinuation of study therapy will be counted
	Subsequent anti-cancer therapy prior to events	Treatment Policy Strategy	Progression, Recurrence or death after subsequent anti-cancer therapy will be counted
	Surgery cancelled or abandoned due to other than progression disease, worsening disease or unresectable tumour	Treatment Policy Strategy	Progression or death that occurs post- planned surgery will be counted
	Secondary primary cancer	While on treatment Strategy	Observations that occur post-secondary primary cancer will be excluded/censored. (EFS censored on the date of last evaluable tumour assessment or surgery conducted prior or on the date of secondary primary cancer identified by BICR
Population-level Summary	Hazard ratio estimated by stratified Cox proportional hazard model		

Estimand for key secondary objective

The main estimand corresponding to the key secondary objectives are HR based on Cox PH stratified by tumour histology (squamous vs non-squamous), NSCLC Stage (II vs III) and PD L1 status (≥1% vs <1% vs indeterminate/not evaluable) in OS between Nivo+Chemo neoadjuvant followed by surgery and Nivolumab adjuvant vs. Placebo+Chemo neoadjuvant followed by surgery and placebo adjuvant in patients with Resectable early stage (Stage IIA [> 4 cm] to IIIB [T3N2 or T4N2]) NSCLC.

Table 9. Summary of Attributes of the Estimand for Secondary Objective

Attribute	Definition Details

Treatment	Nivo+Chemo neoadjuvant followed by surgery and Nivolumab adjuvant vs. Placebo+Chemo neoadjuvant followed by surgery and placebo adjuvant		
Population	Patients with Resectable early stage (Stage IIA [> 4 cm] to IIIB [T3N2 or T4N2]) NSCLC		
Variable	Overall survival OS, defined as the time between the date of randomization and the date of death due to any cause.		
Intercurrent Events (ICEs)	**Event**	**Strategy**	**Description**
	Discontinuation of study therapy	Treatment Policy Strategy	Death that occurs after discontinuation of study therapy will be counted
	Start of subsequent anti- cancer therapy	Treatment Policy Strategy	Death that occurs after initiation of subsequent anticancer therapy will be counted.
Population-level Summary	Hazard ratio estimated by stratified Cox proportional hazard model		

Supportive analyses of EFS

The following supportive analyses were planned to be conducted in the randomized subjects:

- EFS will be compared between treatment groups via a 2-sided max-combo test. The max-combo test statistic from the Fleming-Harrington family of test statistics. To examine the assumption of proportional hazards in the Cox regression model, in addition to treatment, a time-dependent variable defined by treatment by time interaction will be added into the model. A two-sided Wald Chi-square p-value of less than 0.1 may indicate a potential non constant treatment effect.

  The estimates of the EFS hazard ratios will be estimated in 2 periods. The periods will be defined by a cut-off point. The cut-off point will be calculated using a stratified time-dependent Cox model with effects for treatment and period-by-treatment interaction.

- A multivariate Cox regression model will be used in order to estimate the treatment effect after adjustment for possible imbalances in known or potential prognostic factors.

- EFS per BICR using stratification factors as obtained from the baseline CRF pages (instead of IRT). This analysis will be performed only if at least one stratification variable/factor at randomization (as per IRT) and baseline are not concordant for at least 10% of the randomized subjects.

- The primary EFS based on BICR assessments analysis will be repeated using secondary EFS definition which accounts for the tumour scans post subsequent therapies for the primary efficacy population.

- Due to supply chain constraints and operational challenges, BMS has discontinued all BMS-Sponsored clinical trials in Russia by the end of June 2022. In order to assess the potential impact of Russia exit, the primary EFS based on BICR assessments analysis will be repeated using population excluding patients from Russia.

- EFS per BICR accounting for missing tumour assessment prior to EFS event (progression/recurrence or death). This analysis will be performed only if at least 10% of events have missing prior tumour assessment.

- EFS based on investigator assessments. It is to be noted that per CRF instruction, the investigator will not consider a second primary cancer as a recurrence/progression.
- EFS per BICR using an un-stratified Cox model. The hazard ratio associated with treatment will be presented along with the associated two-sided 95% CIs.
- EFS per BICR for randomized subjects without relevant protocol deviations. This analysis will be conducted only if there are more than 10% subjects with relevant protocol deviations.
- In order to assess the potential impact of the change in tumour assessment scheduled on the longer term and potential missing assessments, EFS (primary definition by BICR) will also be analysed based on interval censoring method.

Supportive analyses for OS

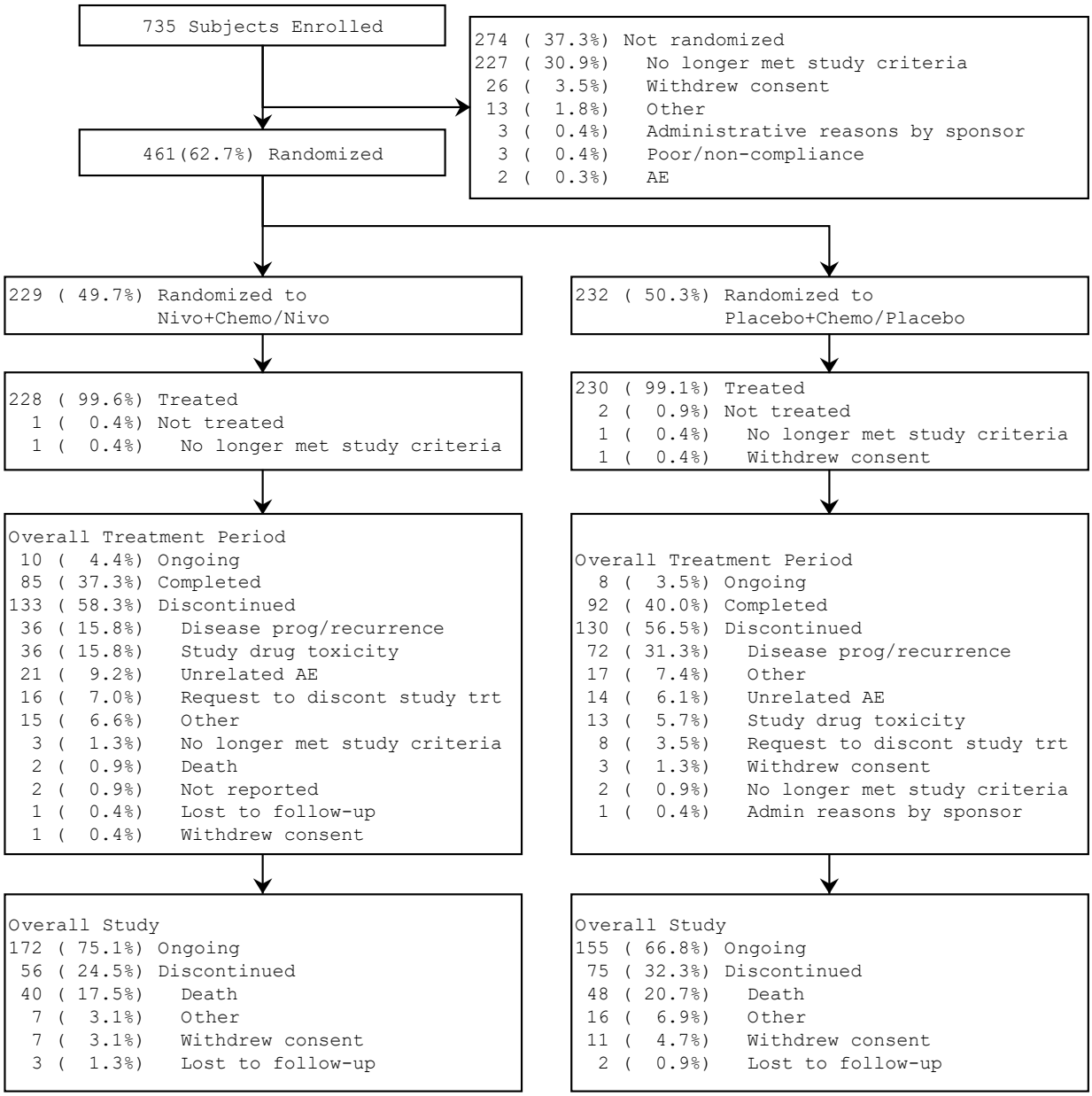
The following supportive analyses will be conducted in the randomized subjects:

- A multivariate Cox regression model will be used in order to estimate the treatment effect after adjustment for possible imbalances in known or potential prognostic factors.
- OS using an un-stratified Cox model. The hazard ratio associated with treatment will be presented along with the associated two-sided 95% CIs.
- OS analysis using stratification factors as obtained from the baseline CRF pages or database (instead of IRT). This analysis will be performed only if the stratification variable/factor at randomization (as per IRT) and baseline are discordant for at least 10% of randomized subjects.
- OS analysis for participants with no relevant deviation. This analysis will be conducted only if there are more than 10% participants with relevant protocol deviations.
- In order to assess the potential impact of Russia exit, the OS analysis will be repeated using population excluding patients from Russia.

Results

Participant flow

Figure 3. Subject disposition during the overall study - Global Population



Other reasons for discontinuation from the overall treatment period included closure of the Russian sites (due to the Russian/Ukrainian political crisis), worsening of pulmonary function/performance status making the subject no longer eligible for surgery.

Other reasons for discontinuation from the overall study were mainly due to closure of the Russian sites (due to the Russian/Ukrainian political crisis).

Table 10. Subject Disposition by Period - Subjects in the Global Population

Neoadjuvant Period: All Treated Subjects in Global Population

	Number of Subjects (%)		
Status (%)	Arm A Nivo+Chemo/Nivo N = 228	Arm B Placebo+Chemo/Placebo N = 230	Total N = 458
ONGOING NEOADJUVANT TREATMENT	0	0	0
COMPLETED NEOADJUVANT TREATMENT	194 (85.1)	205 (89.1)	399 (87.1)
DISCONTINUED NEOADJUVANT TREATMENT	34 (14.9)	25 (10.9)	59 (12.9)
REASON FOR DISCONTINUATION OF NEOADJUVANT TREATMENT			
DISEASE PROGRESSION/RECURRENCE	3 (1.3)	3 (1.3)	6 (1.3)
STUDY DRUG TOXICITY	21 (9.2)	11 (4.8)	32 (7.0)
ADVERSE EVENT UNRELATED TO STUDY DRUG	6 (2.6)	4 (1.7)	10 (2.2)
SUBJECT REQUEST TO DISCONTINUE TREATMENT	2 (0.9)	3 (1.3)	5 (1.1)
SUBJECT WITHDREW CONSENT	0	1 (0.4)	1 (0.2)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (0.4)	2 (0.9)	3 (0.7)
OTHER	1 (0.4)	1 (0.4)	2 (0.4)
DISCONTINUED NEOADJUVANT TREATMENT DUE TO COVID-19 (AE UNRELATED TO STUDY DRUG)	0	1 (0.4)	1 (0.2)

Definitive Surgery: All Randomized Subjects in Global Population

	Arm A Nivo+Chemo/Nivo N = 229	Arm B Placebo+Chemo/Placebo N = 232
SUBJECTS WITH DEFINITIVE SURGERY (%)	178 (77.7)	178 (76.7)
SUBJECTS WITH CANCELLED DEFINITIVE SURGERY (%)	46 (20.1)	50 (21.6)
REASON FOR CANCELLED SURGERY		
SUBJECT REFUSAL	11/46 (23.9)	8/50 (16.0)
SURGEON DECISION	8/46 (17.4)	6/50 (12.0)
WORSENING OF DISEASE PRECLUDING SURGERY	5/46 (10.9)	4/50 (8.0)
RADIOGRAPHIC PROGRESSION PRECLUDING SURGERY	8/46 (17.4)	18/50 (36.0)
ADVERSE EVENT	7/46 (15.2)	4/50 (8.0)
OTHER	7/46 (15.2)	10/50 (20.0)
SUBJECTS WITH SURGERY ABANDONED (%)	3 (1.3)	4 (1.7)
REASON FOR SURGERY ABANDONED (a)		
UNRESECTABLE TUMOR OR WORSENING OF DISEASE	2 (66.7)	3 (75.0)
OTHER	1 (33.3)	1 (25.0)

Definitive Surgery: All Subjects in Global Population with Surgery but no Adjuvant Therapy Treatment

Status (%)	Arm A Nivo+Chemo/Nivo N = 39	Arm B Placebo+Chemo/Placebo N = 29	Total N = 68
REASON FOR NO CONTINUATION ADJUVANT TREATMENT			
DISEASE PROGRESSION/RECURRENCE	5 (12.8)	14 (48.3)	19 (27.9)
STUDY DRUG TOXICITY	13 (33.3)	5 (17.2)	18 (26.5)
DEATH	2 (5.1)	0	2 (2.9)
ADVERSE EVENT UNRELATED TO STUDY DRUG	7 (17.9)	4 (13.8)	11 (16.2)
SUBJECT REQUEST TO DISCONTINUE TREATMENT	5 (12.8)	4 (13.8)	9 (13.2)
SUBJECT WITHDREW CONSENT	0	1 (3.4)	1 (1.5)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (2.6)	0	1 (1.5)
LOST TO FOLLOW-UP	1 (2.6)	0	1 (1.5)
OTHER	4 (10.3)	1 (3.4)	5 (7.4)
NOT REPORTED	1 (2.6)	0	1 (1.5)

Adjuvant Period: All Subjects in Global Population with Adjuvant Therapy Treatment

Status (%)	Arm A Nivo+Chemo/Nivo N = 142	Arm B Placebo+Chemo/Placebo N = 152	Total N = 294
ONGOING ADJUVANT TREATMENT	8 (5.6)	8 (5.3)	16 (5.4)
COMPLETED ADJUVANT TREATMENT	85 (59.9)	92 (60.5)	177 (60.2)
DISCONTINUED ADJUVANT TREATMENT	49 (34.5)	52 (34.2)	101 (34.4)
REASON FOR DISCONTINUATION OF ADJUVANT TREATMENT			
DISEASE PROGRESSION/RECURRENCE	16 (11.3)	37 (24.3)	53 (18.0)
STUDY DRUG TOXICITY	17 (12.0)	3 (2.0)	20 (6.8)
ADVERSE EVENT UNRELATED TO STUDY DRUG	8 (5.6)	5 (3.3)	13 (4.4)
SUBJECT REQUEST TO DISCONTINUE TREATMENT	3 (2.1)	1 (0.7)	4 (1.4)
SUBJECT WITHDREW CONSENT	1 (0.7)	0	1 (0.3)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (0.7)	0	1 (0.3)
OTHER	3 (2.1)	6 (3.9)	9 (3.1)
DISCONTINUED ADJUVANT TREATMENT DUE TO COVID-19 (AE UNRELATED TO STUDY DRUG)	1 (0.7)	0	1 (0.3)

[a] Denominator based on number of subjects with surgery abandoned.

Recruitment

461 subjects were randomized (229 to the nivo+chemo/nivolumab arm and 232 to the placebo+chemo/placebo arm) at 86 sites in 18 countries: Argentina, Australia, Belgium, Brazil, China, Czech Republic, France, Germany, Italy, Japan, Mexico, Netherlands, Poland, Romania, Russian Federation, Spain, Taiwan, United States.

First subject's randomization date: 20 November 2019

Last subject's randomization date: 05 April 2022

Clinical data cut-off date: 26 July 2023

Database lock date: 06 September 2023

Minimum follow-up: 15.7 months

Median follow-up: 25.4 months

Conduct of the study

Protocol amendments

The original protocol for this study was dated 26-Mar-2019. As of the clinical data cut-off (26-Jul-2023), there were 3 global revisions (which include 2 revised protocols and protocol Amendment 03).

There were 2 country-specific amendments: Protocol Amendment 01 (China; dated 26-Mar-2019) that added a China substudy and Protocol Amendment 01 (EU; dated 25-Jan-2023) that added country-specific differences for Germany, Romania and Czech Republic to comply with European Union Clinical Trial Regulation requirements. In addition, there were 6 administrative letters.

Table 11. Summary of Key Changes to Global Protocol CA20977T

Document Date	Summary of Key Changes	Planned Sample Size	No. of Randomized Subjects at the Time of the Amendment
Revised Protocol 01 20-Dec-2019	Modified the objectives, endpoints, and definitions to fulfil Health Authority requests. – Added EFS and OS comparisons by tumour PD-L1 status as an exploratory objective. – Moved safety and tolerability from an exploratory objective to a secondary objective. – Updated endpoint definitions. – Removed exploratory endpoints from the synopsis. Added additional chemo regimens. Added instructions for subjects to follow local regulations for pregnancy testing and contraceptive use. Updated the imaging assessments and biomarker collections.	452	4
Revised Protocol 02 11-May-2020	Updated tumour PD-L1 stratification from ≥1% or < 1% which includes indeterminate or not evaluable to PD-L1 ≥1% or < 1% or indeterminate or not evaluable per health authority request. Clarified the inclusion criteria for tumour eligibility: Subjects with N3 nodal disease were not eligible. Subjects with resectable T4 tumour size with Stage IIIA or IIIB disease could have been reviewed and approved for participation in the study by the multidisciplinary team (including surgeon, medical oncologist, radiation oncologist, etc). Updated the survival status window and collection of EQ-5D-3L outcomes by phone. Updated the window for preoperative imaging assessment. Clarified instructions when subjects did not receive surgery. Removed carboplatin + docetaxel as a chemo regimen for subjects with SQ histology. Added CYP3A4 inhibitors as prohibited medications when treated with docetaxel. For docetaxel, added dose reduction for subjects with impaired renal function, treatment delay when total bilirubin > ULN, and discontinuation for cystoid macular oedema.	452	24
Protocol Amendment 03[a] 20-Apr-2021	Updated the requirement for tumour tissue submission at screening, upon progression, or recurrence of disease. Aligned the language for EFS throughout the document. Clarified imaging requirements and definitions for the neoadjuvant setting. Added SARS-CoV-2 serology samples. Added AE/SAE collection to collect SARS-CoV-2 related events.	452	188

[a] Effective Oct-2020, a companywide change occurred regarding the presentation of protocol revisions. All global revisions were given amendment numbers instead of revision numbers.

Protocol deviations

Important protocol deviations

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's

rights, safety, or well-being. The MAH modified the terminology, reporting process, and categorization of protocol deviations. As this study was ongoing at the time of the effective date of the updated procedure for reporting and classifying protocol deviations, both important and significant deviations have been provided.

Review of the important protocol deviations across both treatment arms revealed the highest volume in 3 categories: Trial Procedures, Study Intervention (Study Treatment), and Informed Consent and/or Ethics.

- Trial Procedures (333 deviations): mainly included trial assessments being performed outside of the required window and/or missed assessments.
- Study Intervention (Study Treatment) (223 deviations): mainly included incorrect study treatment assignment or randomization error (incorrect stratification), incorrect study dosing/treatment compliance (i.e., dosing was done out of window), or subjects were treated outside of the required time frame from randomization.
- Informed Consent (69 deviations): mainly included new study procedures that may have been performed before a subject was reconsented or the reconsent containing the updated risk language or safety information was not signed or signed with delay.

Table 12. Important Protocol Deviations - All Enrolled Subjects in the Global Population

Important Protocol Deviations Category	Arm A: Nivo+Chemo/Nivolumab	Arm B: Placebo+Chemo/Placebo	Total
TOTAL NUMBER OF DEVIATIONS	364	377	741
INCLUSION/EXCLUSION CRITERIA	12	25	37
INFORMED CONSENT AND/OR ETHICS (IEC/IRB)	41	28	69
PROHIBITED CONCOMITANT MEDICATION	30	18	48
SAFETY REPORTING	16	12	28
STUDY INTERVENTION (STUDY TREATMENT)	107	116	223
TRIAL PROCEDURES	157	176	333
DISCONTINUATION	1	2	3

The sum of all deviations is reported per category as a subject may have more than 1 deviation.

Relevant protocol deviations

Relevant protocol deviations are important protocol deviations that could affect the interpretability of key study results; they are programmable deviations from the clinical database that are protocol-specific.

Table 13. Relevant Protocol Deviations - All Randomized Subjects in Global Population

	Number of Subjects (%)		
Total	Arm A Nivolumab + Chemo/Nivolumab N = 229	Arm B Placebo + Chemo/Placebo N = 232	N = 461
SUBJECTS WITH AT LEAST ONE DEVIATION	4 (1.7)	7 (3.0)	11 (2.4)
AT ENTRANCE			
SUBJECT WITH INADEQUATE DISEASE STAGE	2 (0.9)	4 (1.7)	6 (1.3)
SUBJECT WITH ANY PRIOR ANTI-CANCER THERAPIES FOR NSCLC	1 (0.4)	0	1 (0.2)
SUBJECT WITH BASELINE ECOG PS>1	0	1 (0.4)	1 (0.2)
ON-TREATMENT DEVIATIONS			
SUBJECT RECEIVING PROHIBITED CONCOMITANT MEDICATION OR PROCEDURE	1 (0.4)	2 (0.9)	3 (0.7)

Baseline data

Table 14. Baseline Characteristics - All Randomized Subjects in the Global Population

	Arm A Nivolumab + Chemo/Nivolumab	Arm B Placebo + Chemo/Placebo	Total
	N = 229	N = 232	N = 461
AGE (YEARS)			
N	229	232	461
MEAN	64.2	64.6	64.4
MEDIAN	66.0	66.0	66.0
MIN , MAX	37, 83	35, 86	35, 86
Q1 , Q3	60.0, 70.0	60.0, 71.0	60.0, 70.0
SD	7.9	8.4	8.1
AGE CATEGORIZATION 1(%)			
< 65	102 (44.5)	100 (43.1)	202 (43.8)
>= 65	127 (55.5)	132 (56.9)	259 (56.2)
AGE CATEGORIZATION 2(%)			
< 65	102 (44.5)	100 (43.1)	202 (43.8)
>= 65 AND < 75	115 (50.2)	113 (48.7)	228 (49.5)
>= 75	12 (5.2)	19 (8.2)	31 (6.7)
AGE CATEGORIZATION 3(%)			
< 65	102 (44.5)	100 (43.1)	202 (43.8)
>= 65 AND < 75	115 (50.2)	113 (48.7)	228 (49.5)
>= 75 AND < 85	12 (5.2)	18 (7.8)	30 (6.5)
>= 85	0	1 (0.4)	1 (0.2)
SEX (%)			
MALE	167 (72.9)	160 (69.0)	327 (70.9)
FEMALE	62 (27.1)	72 (31.0)	134 (29.1)
RACE (%)			
WHITE	155 (67.7)	175 (75.4)	330 (71.6)
BLACK OR AFRICAN AMERICAN	4 (1.7)	4 (1.7)	8 (1.7)
ASIAN	66 (28.8)	50 (21.6)	116 (25.2)
ASIAN INDIAN	1 (0.4)	0	1 (0.2)
CHINESE	25 (10.9)	22 (9.5)	47 (10.2)
JAPANESE	40 (17.5)	28 (12.1)	68 (14.8)
OTHER	4 (1.7)	3 (1.3)	7 (1.5)
ETHNICITY (%)			
HISPANIC OR LATINO	9 (3.9)	17 (7.3)	26 (5.6)
NOT HISPANIC OR LATINO	128 (55.9)	113 (48.7)	241 (52.3)
NOT REPORTED	92 (40.2)	102 (44.0)	194 (42.1)
GEOGRAPHIC REGION (%)			
NORTH AMERICA	23 (10.0)	21 (9.1)	44 (9.5)
EUROPE	123 (53.7)	127 (54.7)	250 (54.2)
ASIA	65 (28.4)	50 (21.6)	115 (24.9)
REST OF WORLD	18 (7.9)	34 (14.7)	52 (11.3)
DISEASE STAGE AT STUDY ENTRY (CRF)			
STAGE IIA	15 (6.6)	18 (7.8)	33 (7.2)
STAGE IIB	66 (28.8)	63 (27.2)	129 (28.0)
STAGE IIIA	103 (45.0)	114 (49.1)	217 (47.1)
STAGE IIIB	43 (18.8)	35 (15.1)	78 (16.9)
STAGE IIIC	2 (0.9)	0	2 (0.4)
STAGE IV	0	2 (0.9)	2 (0.4)
CELL TYPE AT STUDY ENTRY			
SQUAMOUS CELL CARCINOMA	116 (50.7)	118 (50.9)	234 (50.8)
NON-SQUAMOUS CELL CARCINOMA	113 (49.3)	114 (49.1)	227 (49.2)
ADENOCARCINOMA	109 (47.6)	102 (44.0)	211 (45.8)
LARGE CELL CARCINOMA	1 (0.4)	3 (1.3)	4 (0.9)
BRONCHO-ALVEOLAR CARCINOMA	0	1 (0.4)	1 (0.2)
OTHER	3 (1.3)	8 (3.4)	11 (2.4)

SMOKING STATUS			
NEVER SMOKER	17 (7.4)	27 (11.6)	44 (9.5)
CURRENT/FORMER	212 (92.6)	205 (88.4)	417 (90.5)
BASELINE ECOG PS			
0	147 (64.2)	141 (60.8)	288 (62.5)
1	82 (35.8)	91 (39.2)	173 (37.5)
BASELINE WEIGHT (KG)			
N	229	232	461
MEAN	77.40	74.94	76.16
MEDIAN	75.70	73.80	75.00
MIN , MAX	35.3, 150.1	37.4, 128.0	35.3, 150.1
SD	17.35	17.66	17.53
TIME FROM INITIAL NSCLC DIAGNOSIS TO RANDOMIZATION (MONTHS)			
N	229	232	461
MEAN	1.46	1.73	1.60
MEDIAN	1.31	1.31	1.31
MIN , MAX	0.2, 5.0	0.0, 15.2	0.0, 15.2
SD	0.72	1.57	1.23
TIME FROM INITIAL NSCLC DIAGNOSIS TO RANDOMIZATION (%)			
< 1 MONTH	63 (27.5)	55 (23.7)	118 (25.6)
1- < 2 MONTHS	126 (55.0)	115 (49.6)	241 (52.3)
2- < 3 MONTHS	29 (12.7)	45 (19.4)	74 (16.1)
3- < 4 MONTHS	10 (4.4)	12 (5.2)	22 (4.8)
4- < 5 MONTHS	1 (0.4)	2 (0.9)	3 (0.7)
>= 5 MONTHS	0	3 (1.3)	3 (0.7)
PD-L1 (CLINICAL DATABASE)			
<1%	93 (40.6)	93 (40.1)	186 (40.3)
>=1%	128 (55.9)	128 (55.2)	256 (55.5)
1-49%	83 (36.2)	76 (32.8)	159 (34.5)
>=50%	45 (19.7)	52 (22.4)	97 (21.0)
NOT EVALUABLE	8 (3.5)	11 (4.7)	19 (4.1)

North America: US, **Europe:** Belgium, Czech Republic, France, Germany, Italy, Netherlands, Poland, Romania, Russian Federation, Spain; **Asia:** China, Japan, Taiwan; **Rest of World:** Argentina, Australia, Brazil, Mexico

Table 15. Baseline Demographic and Disease Characteristics Summary - All Randomized Subjects in the Global Population with Quantifiable PD-L1 Expression ≥1%

	PD-L1 ≥ 1%	
	Arm A: Nivolumab +Chemo/Nivo N = 128	**Arm B: Nivolumab +Placebo/Placebo N = 128**
AGE (YEARS)		
MEAN	64.3	65
MEDIAN	66	66
MIN , MAX	47 , 78	35 , 86
Q1 , Q3	59.5 , 70.0	59.5 , 71.0
SD	7.58	8.47
AGE CATEGORIZATION 1 (%)		
< 65	60 (46.9)	55 (43.0)
≥ 65	68 (53.1)	73 (57.0)
AGE CATEGORIZATION 2 (%)		
< 65	60 (46.9)	55 (43.0)
≥ 65 AND < 75	61 (47.7)	61 (47.7)
≥ 75	7 (5.5)	12 (9.4)
AGE CATEGORIZATION 3 (%)		
< 65	60 (46.9)	55 (43.0)
≥ 65 AND < 75	61 (47.7)	61 (47.7)
≥ 75 AND < 85	7 (5.5)	11 (8.6)
≥ 85	0	1 (0.8)
SEX (%)		
MALE	97 (75.8)	94 (73.4)
FEMALE	31 (24.2)	34 (26.6)
RACE (%)		
WHITE	84 (65.6)	92 (71.9)
BLACK OR AFRICAN AMERICAN	2 (1.6)	3 (2.3)
ASIAN	40 (31.3)	32 (25.0)
ASIAN INDIAN	1 (0.8)	0
CHINESE	17 (13.3)	15 (11.7)
JAPANESE	22 (17.2)	17 (13.3)
OTHER	2 (1.6)	1 (0.8)
ETHNICITY (%)		
HISPANIC OR LATINO	4 (3.1)	10 (7.8)
NOT HISPANIC OR LATINO	73 (57.0)	63 (49.2)
NOT REPORTED	51 (39.8)	55 (43.0)
COUNTRY BY GEOGRAPHIC REGION (%)		
NORTH AMERICA	13 (10.2)	13 (10.2)
UNITED STATES	13 (10.2)	13 (10.2)
EUROPE	68 (53.1)	64 (50.0)
BELGIUM	4 (3.1)	5 (3.9)
CZECH REPUBLIC	12 (9.4)	9 (7.0)
FRANCE	10 (7.8)	7 (5.5)
GERMANY	16 (12.5)	12 (9.4)
ITALY	0	3 (2.3)
NETHERLANDS	3 (2.3)	4 (3.1)
POLAND	2 (1.6)	2 (1.6)
ROMANIA	5 (3.9)	5 (3.9)
RUSSIAN FEDERATION	13 (10.2)	13 (10.2)
SPAIN	3 (2.3)	4 (3.1)
ASIA	39 (30.5)	32 (25.0)
CHINA	16 (12.5)	14 (10.9)
JAPAN	22 (17.2)	17 (13.3)
TAIWAN	1 (0.8)	1 (0.8)
REST OF WORLD	8 (6.3)	19 (14.8)
ARGENTINA	2 (1.6)	6 (4.7)
AUSTRALIA	2 (1.6)	1 (0.8)
BRAZIL	2 (1.6)	10 (7.8)
MEXICO	2 (1.6)	2 (1.6)

	PD-L1 ≥ 1%	
	Arm A: Nivolumab +Chemo/Nivo N = 128	**Arm B: Nivolumab +Placebo/Placebo N = 128**
DISEASE STAGE AT STUDY ENTRY (CRF)		
STAGE IIA	8 (6.3)	13 (10.2)
STAGE IIB	40 (31.3)	32 (25.0)
STAGE IIIA	57 (44.5)	57 (44.5)
STAGE IIIB	22 (17.2)	24 (18.8)
STAGE IIIC	1 (0.8)	0
STAGE IV	0	2 (1.6)
CELL TYPE AT STUDY ENTRY		
SQUAMOUS CELL CARCINOMA	79 (61.7)	78 (60.9)
NON-SQUAMOUS CELL CARCINOMA	49 (38.3)	50 (39.1)
ADENOCARCINOMA	48 (37.5)	44 (34.4)
LARGE CELL CARCINOMA	1 (0.8)	0
BRONCHO-ALVEOLAR CARCINOMA	0	1 (0.8)
OTHER	0	5 (3.9)
SMOKING STATUS		
NEVER SMOKER	6 (4.7)	18 (14.1)
CURRENT/FORMER	122 (95.3)	110 (85.9)
UNKNOWN	0	0
BASELINE ECOG PS		
0	76 (59.4)	76 (59.4)
1	52 (40.6)	52 (40.6)
BASELINE WEIGHT (KG)		
MEAN	76.96	74.18
MEDIAN	75.7	74
MIN , MAX	35.3 , 150.1	42.0 , 128.0
SD	17.436	16.598
TIME FROM INITIAL NSCLC DIAGNOSIS TO RANDOMIZATION (MONTHS)		
MEAN	1.42	1.74
MEDIAN	1.28	1.31
MIN , MAX	0.4 , 3.7	0.0 , 15.2
SD	0.682	1.707
TIME FROM INITIAL NSCLC DIAGNOSIS TO RANDOMIZATION (%)		
< 1 MONTH	37 (28.9)	32 (25.0)
1- < 2 MONTHS	69 (53.9)	65 (50.8)
2- < 3 MONTHS	17 (13.3)	21 (16.4)
3- < 4 MONTHS	5 (3.9)	8 (6.3)
4- < 5 MONTHS	0	0
≥ 5 MONTHS	0	2 (1.6)
PD-L1 (CLINICAL DATABASE)		
≥ 1%	128 (100.0)	128 (100.0)
1-49%	83 (64.8)	76 (59.4)
≥ 50%	45 (35.2)	52 (40.6)

Surgical details

Table 16. Definitive Surgery - All Randomized Subjects in the Global Population

	Number of Subjects (%)	
	Arm A Nivolumab + Chemo/Nivolumab N = 229	Arm B Placebo + Chemo/Placebo N = 232
DISEASE STAGE PRIOR TO DEFINITIVE SURGERY (%)		
STAGE 0	7 (3.1)	5 (2.2)
STAGE IA	52 (22.7)	30 (12.9)
STAGE IB	16 (7.0)	23 (9.9)
STAGE IIA	10 (4.4)	21 (9.1)
STAGE IIB	46 (20.1)	39 (16.8)
STAGE IIIA	57 (24.9)	70 (30.2)
STAGE IIIB	11 (4.8)	13 (5.6)
STAGE IVA	3 (1.3)	5 (2.2)
STAGE IVB	2 (0.9)	2 (0.9)
NOT REPORTED	25 (10.9)	24 (10.3)
SUBJECTS WITH CLINICAL DOWNSTAGING (1) (%)	118 (51.5)	102 (44.0)

SUBJECTS WITH DEFINITIVE SURGERY NOT REPORTED (%)	2 (0.9)	0
SUBJECTS WITH CANCELLED DEFINITIVE SURGERY (%)	46 (20.1)	50 (21.6)
REASON FOR CANCELLED SURGERY (2)		
SUBJECT REFUSAL	11 (23.9)	8 (16.0)
SURGEON DECISION	8 (17.4)	6 (12.0)
WORSENING OF DISEASE PRECLUDING SURGERY	5 (10.9)	4 (8.0)
RADIOGRAPHIC PROGRESSION PRECLUDING SURGERY	8 (17.4)	18 (36.0)
ADVERSE EVENT	7 (15.2)	4 (8.0)
OTHER	7 (15.2)	10 (20.0)
SUBJECTS WITH SURGERY ABANDONED (%)	3 (1.3)	4 (1.7)
REASON FOR SURGERY ABANDONED (3)		
UNRESECTABLE TUMOR OR WORSENING OF DISEASE	2 (66.7)	3 (75.0)
OTHER	1 (33.3)	1 (25.0)
SUBJECTS WITH DEFINITIVE SURGERY (%)	178 (77.7)	178 (76.7)
SUBJECTS WITH DELAYED SURGERY (4) (7) (%)	36 (20.2)	33 (18.5)
REASON FOR DELAYED SURGERY (4) (5)		
ADVERSE EVENT	8 (22.2)	7 (21.2)
LOGISTICAL ISSUE	8 (22.2)	11 (33.3)
SUBJECT DECISION	4 (11.1)	3 (9.1)
OTHER	12 (33.3)	10 (30.3)
NOT REPORTED	4 (11.1)	2 (6.1)
LENGTH OF DELAY (WEEKS)		
N	36	33
MEAN	3.3	2.5
MEDIAN	1.7	1.1
MIN , MAX	0 , 20	0 , 11
Q1 , Q3	0.6 , 3.0	0.4 , 2.9
STANDARD DEVIATION	5.0	2.9
LENGTH OF DELAY (5)		
<= 2 WEEKS	20 (55.6)	21 (63.6)
> 2 AND <= 4 WEEKS	9 (25.0)	4 (12.1)
> 4 AND <= 6 WEEKS	2 (5.6)	3 (9.1)
> 6 WEEKS	5 (13.9)	5 (15.2)
DURATION OF SURGERY (MINUTES)		
N	156	150
MEAN	237.0	232.9
MEDIAN	216.5	223.0
MIN , MAX	49 , 613	25 , 496
Q1 , Q3	164.0 , 300.0	150.0 , 299.0
STANDARD DEVIATION	103.4	97.9
LENGTH OF HOSPITAL STAY (DAYS)		
N	170	168
MEAN	10.9	10.4
MEDIAN	9.0	9.0
MIN , MAX	1 , 41	2 , 121
Q1 , Q3	6.0 , 13.0	6.0 , 12.0
STANDARD DEVIATION	7.2	10.4
LENGTH OF ICU STAY (DAYS)		
N	90	66
MEAN	2.6	3.5
MEDIAN	2.0	2.0
MIN , MAX	0 , 33	1 , 43
Q1 , Q3	1.0 , 3.0	1.0 , 4.0
STANDARD DEVIATION	3.8	6.1
METHOD OF SURGERY (7) (%)		
SURGERY ASSISTED BY ROBOTIC TECHNOLOGY		
YES	28 (15.7)	27 (15.2)
NO	150 (84.3)	151 (84.8)
SURGICAL APPROACH CONVERSION		
YES	12 (6.7)	9 (5.1)
NO	166 (93.3)	169 (94.9)
SURGICAL APPROACH CONVERSION		
VATS TO OPEN	10 (5.6)	8 (4.5)
ROBOTIC TO VATS	0	1 (0.6)
ROBOTIC TO OPEN	2 (1.1)	0
CONVERSION TYPE		
ELECTIVE	11 (6.2)	7 (3.9)
EMERGENT	1 (0.6)	2 (1.1)

CONVERSION REASON		
VASCULAR	1 (0.6)	3 (1.7)
ANATOMY	6 (3.4)	4 (2.2)
LYMPH NODES	3 (1.7)	2 (1.1)
TECHNICAL	2 (1.1)	0
TYPE OF SURGERY (6) (7) (%)		
WEDGE RESECTION	1 (0.6)	2 (1.1)
SEGMENTECTOMY	2 (1.1)	0
SINGLE LOBECTOMY	142 (79.8)	128 (71.9)
BI-LOBECTOMY	14 (7.9)	23 (12.9)
PNEUMONECTOMY	16 (9.0)	24 (13.5)
OTHER	3 (1.7)	1 (0.6)
SURGERY OUTCOME (7) (%)		
R0	159 (89.3)	161 (90.4)
R1	17 (9.6)	11 (6.2)
R2	2 (1.1)	6 (3.4)

(1) Subjects with clinical downstaging have lower disease stage prior to surgery vs baseline.

(2) Denominator based on number of subjects with cancelled surgery.

(3) Denominator based on number of subjects with surgery abandoned.

(4) Time from last neoadjuvant dose to surgery > 6 weeks

(5) Denominator based on number of subjects with delayed surgery.

(6) Subjects may have more than 1 surgery type.

(7) Denominator based on number of subjects with surgery

Subsequent cancer therapy

Table 17 Subsequent Cancer Therapy - All Randomized Subjects in Global Population

	Number of Subjects (%)	
	Arm A Nivo+Chemo/Nivolumab N = 229	Arm B Placebo+Chemo/Placebo N = 232
SUBJECTS WITH ANY SUBSEQUENT THERAPY (1)	67 (29.3)	101 (43.5)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY	43 (18.8)	63 (27.2)
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY	7 (3.1)	15 (6.5)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY	50 (21.8)	87 (37.5)
ANTI-CTLA4	4 (1.7)	5 (2.2)
IPILIMUMAB	4 (1.7)	4 (1.7)
TREMELIMUMAB	0	1 (0.4)
ANTI-PD1 OR ANTI-PDL1	19 (8.3)	68 (29.3)
ATEZOLIZUMAB	4 (1.7)	8 (3.4)
CAMRELIZUMAB	1 (0.4)	1 (0.4)
DOSTARLIMAB	0	1 (0.4)
DURVALUMAB	1 (0.4)	14 (6.0)
NIVOLUMAB	5 (2.2)	12 (5.2)
PEMBROLIZUMAB	8 (3.5)	34 (14.7)
SINTILIMAB	0	1 (0.4)
TISLELIZUMAB	1 (0.4)	1 (0.4)
TORIPALIMAB	0	1 (0.4)
TQ B2450	1 (0.4)	0
EGFR INHIBITORS		3 (1.3)
AFATINIB	0	1 (0.4)
ERLOTINIB	0	1 (0.4)
NECITUMUMAB	0	1 (0.4)
INVESTIGATIONAL ANTINEOPLASTIC AGENTS	2 (0.9)	0
KRAS INHIBITORS	5 (2.2)	2 (0.9)
MEK NRAS AND BRAF INHIBITOR	0	1 (0.4)
OTHER SYSTEMIC ANTICANCER THERAPY	43 (18.8)	67 (28.9)
PLATINUM COMPOUNDS	30 (13.1)	58 (25.0)
VEGFR TARGETED THERAPY	10 (4.4)	13 (5.6)
UNASSIGNED	2 (0.9)	2 (0.9)

DCO: 11-Nov-2024

Numbers analysed

Table 18. Analysis Populations - All Enrolled Subjects in Global Population

Population	Arm A Nivolumab + Chemo/Nivolumab	Arm B Placebo + Chemo/Placebo	Total
ENROLLED			735
RANDOMIZED	229	232	461
TREATED	228	230	458
ADJUVANT TREATED	142	152	294
SURGERY RECEIVED	178	178	356
SURGERY RECEIVED BUT NOT ADJUVANT TREATED	39	29	68
PD-L1 EVALUABLE	221	221	442

Outcomes and estimation

Primary endpoint: EFS per BICR

Table 19. EFS per BICR, Primary Definition - All Randomized Subjects in the Global Population

	Arm A Nivo+Chemo/Nivo N = 229	Arm B Placebo+Chemo/Placebo N = 232
Primary Endpoint		
Event-Free Survival per BICR, primary definition		
Events, n (%)	76 (33.2)	113 (48.7)
Median EFS (95% CI), mo.[a]	Not Reached (28.94, NA)	18.43 (13.63, 28.06)
HR (97.36% CI)[b]	0.58 (0.42, 0.81); p = 0.00025[c]	
HR (95% CI)[b]	0.58 (0.43, 0.78)	
EFS rates (95% CI), % [a]		
6 months	84.6 (79.1, 88.8)	79.9 (73.8, 84.7)
12 months	73.4 (66.8, 78.9)	59.2 (52.2, 65.6)
18 months	70.2 (63.4, 76.0)	50.0 (42.9, 56.7)

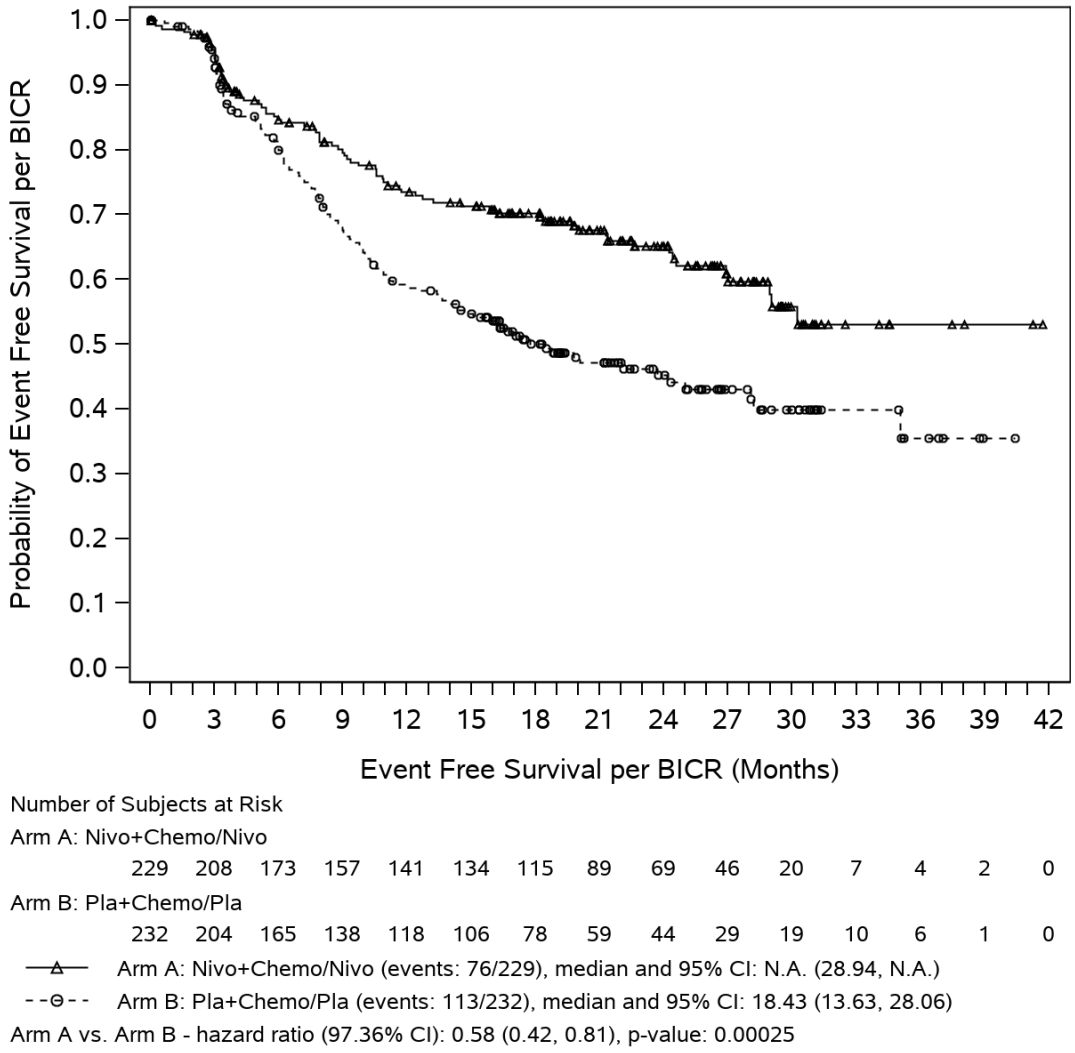
[a] Based on Kaplan-Meier estimates

[b] HR of Arm A to Arm B from a Cox proportional hazard model stratified by randomization stratification factors: tumour PD-L1 status (≥ 1% vs < 1% / NE/indeterminate), disease stage (II vs III), histology (SQ vs NSQ) per IRT

[c] Log-rank test stratified by same factors (per IRT) as used in the Cox proportional hazard model. The p-value threshold for statistical significance was 0.0264.

Clinical data cutoff was 26-Jul-2023. Minimum follow-up (date the last subject was randomized to the date of the clinical data cutoff) was 15.7 months.

Figure 4. Event-Free Survival per BICR, Primary Definition - All Randomized Subjects in the Global Population DCO 26-Jul-2023



Statistical model for hazard ratio and p-value: stratified Cox proportional hazard model and stratified log-rank test. Symbols represent censored observations.

Table 20. Type of Event and Reason for Censoring, EFS per BICR, Primary Definition - All Randomized Subjects in the Global Population DCO 26-Jul-2023

Chemo/Placebo	Arm A: Nivolumab + Chemo/Nivolumab N = 229	Arm B: Placebo + N = 232
NUMBER OF EVENTS (%)	76 (33.2)	113 (48.7)
TYPE OF EVENTS (%)		
PROGRESSION/WORSENING DISEASE PRECLUDING SURGERY (1)	14 (6.1)	22 (9.5)
SURGERY ABANDONED DUE TO UNRESECTABLE TUMOR OR WORSENING OF DISEASE	2 (0.9)	3 (1.3)
PROGRESSION/RECURRENCE AFTER SURGERY (2)	36 (15.7)	77 (33.2)
LOCOREGIONAL	1 (0.4)	1 (0.4)
DISTANT	33 (14.4)	74 (31.9)
NOT REPORTED	2 (0.9)	2 (0.9)
PROGRESSION FOR SUBJECTS WITHOUT SURGERY (2)	7 (3.1)	3 (1.3)

LOCOREGIONAL	6 (2.6)	3 (1.3)
DISTANT	1 (0.4)	0
DEATH	17 (7.4)	8 (3.4)
NUMBER OF SUBJECTS CENSORED (%)	153 (66.8)	119 (51.3)
CENSORED ON DATE OF RANDOMIZATION	4 (1.7)	9 (3.9)
NO ON-STUDY TUMOR ASSESSMENT AND NO DEATH (3)	4 (1.7)	7 (3.0)
NEVER TREATED	1 (0.4)	2 (0.9)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY	1 (0.4)	0
OTHER	2 (0.9)	5 (2.2)
NO ON-STUDY TUMOR ASSESSMENT NOR EVENT PRIOR TO SUBSEQUENT THERAPY	0	2 (0.9)
CENSORED ON DATE OF LAST TUMOR ASSESSMENT OR SURGERY ON-STUDY OR LAST ASSESSMENT OR SURGERY PRIOR TO OR ON SUBSEQUENT ANTI-CANCER THERAPY OR SECONDARY PRIMARY CANCER	149 (65.1)	110 (47.4)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY (4)	14 (6.1)	9 (3.9)
RECEIVED SUBSEQUENT SYSTEMIC THERAPY	6 (2.6)	4 (1.7)
RECEIVED SUBSEQUENT RADIOTHERAPY (5)	8 (3.5)	7 (3.0)
SECONDARY PRIMARY CANCER	0	0
ON STUDY	126 (55.0)	88 (37.9)
STILL ON-NEOADJUVANT TREATMENT	0	0
STILL IN SURGERY PERIOD PHASE	1 (0.4)	0
STILL ON-ADJUVANT TREATMENT	8 (3.5)	7 (3.0)
IN FOLLOW-UP	117 (51.1)	81 (34.9)
OFF STUDY	9 (3.9)	13 (5.6)
LOST TO FOLLOW-UP	1 (0.4)	0
SUBJECT WITHDREW CONSENT	4 (1.7)	3 (1.3)
OTHER	4 (1.7)	10 (4.3)

(1) Progression not necessarily reaching the RECIST 1.1 criteria.

(2) Progression/ recurrence per RECIST 1.1 and/or pathology report

(3) Death occurring after secondary primary cancer or start of subsequent anti-cancer therapy are not considered as events.

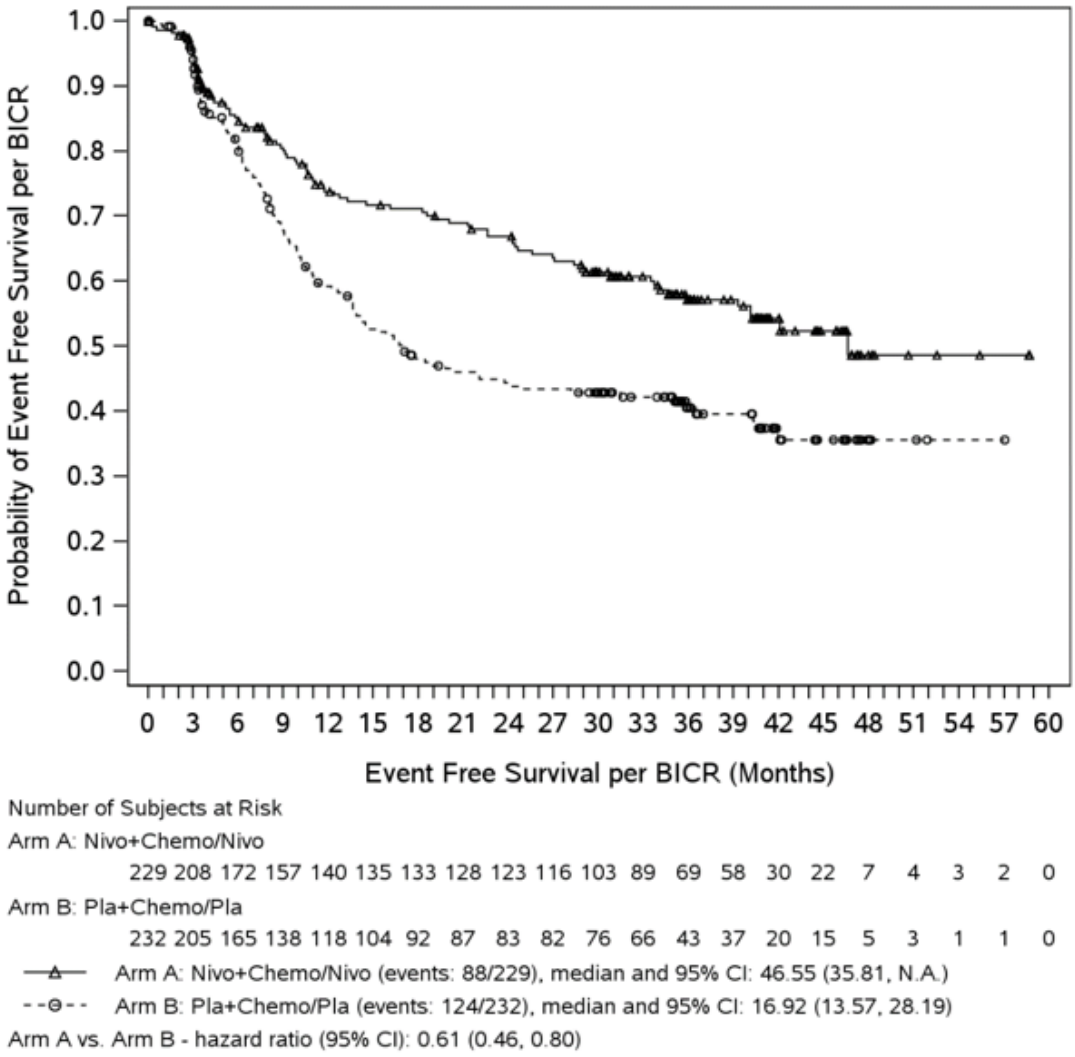
(4) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy (outside of protocol-specified post-operative radiotherapy) without a prior reported EFS event. Those subjects were censored at the last tumour assessment prior to/on start date of subsequent anti-cancer therapy. Subjects may have received more than 1 subsequent anti-cancer therapy type.

(5) Radiotherapy other than protocol defined post-operative radiotherapy.

- Updated analysis (DCO: 11-Nov-2024)

As of a DCO of 11-Nov-2024 (DBL: 16-Apr-2024), with a median follow-up of 41 months, median EFS was 46.55 months in the nivo+chemo/nivolumab arm and 16.92 months in the placebo+chemo/placebo arm [HR = 0.61 (95% CI: 0.46, 0.80)].

Figure 5. Event-Free Survival per BICR, Primary Definition - All Randomized (DCO: 11-Nov-2024)



Statistical model for hazard ratio: stratified Cox proportional hazard model and stratified log-rank test.

Table 21. Event-free Survival Rates per BICR, Primary Definition - All Randomized Subjects in the Global Population (DCO: 11-Nov-2024)

Event Free Survival Rate (95% CI)	Arm A: Nivo + Chemo / Nivo N = 229	Arm B: Placebo + Chemo / Placebo N = 232
6-MONTH	84.6 (79.0, 88.8)	79.9 (73.9, 84.7)
12-MONTH	73.8 (67.2, 79.3)	59.3 (52.2, 65.6)
18-MONTH	71.2 (64.4, 76.9)	48.1 (41.1, 54.8)
24-MONTH	66.9 (59.8, 72.9)	43.9 (36.9, 50.6)
30-MONTH	61.4 (54.1, 67.8)	42.8 (35.9, 49.5)

Based on Kaplan-Meier estimates.

Secondary endpoints

pCR and MPR

Table 22. Pathological Response by BIPR - All Randomized Subjects in the Global Population DCO 26-Jul-2023

	Number of Subjects (%)	
	Arm A Nivolumab + Chemo/Nivolumab N = 229	Arm B Placebo + Chemo/Placebo N = 232
OVERALL:		
COMPLETE PATHOLOGIC RESPONSE (PCR)	58/229 (25.3%)	11/232 (4.7%)
(95% CI) (1)	(19.8, 31.5)	(2.4, 8.3)
DIFFERENCE OF PCR (2, 3)	20.5	
(95% CI)	(14.3, 26.6)	
ESTIMATE OF ODDS RATIO OF PCR (3, 4)	6.64	
(95% CI)	(3.40, 12.97)	
MAJOR PATHOLOGIC RESPONSE (MPR)	81/229 (35.4%)	28/232 (12.1%)
(95% CI) (1)	(29.2, 41.9)	(8.2, 17.0)
DIFFERENCE OF MPR (2, 3)	23.2	
(95% CI)	(15.8, 30.6)	
ESTIMATE OF ODDS RATIO OF MPR (3, 4)	4.01	
(95% CI)	(2.48, 6.49)	
TUMOR REGION:		
COMPLETE PATHOLOGIC RESPONSE		
YES	63 (27.5)	13 (5.6)
NO	94 (41.0)	146 (62.9)
NOT EVALUABLE	11 (4.8)	9 (3.9)
NO SAMPLE AVAILABLE	61 (26.6)	64 (27.6)
NOT RECEIVED SURGERY	50 (21.8)	54 (23.3)
RECEIVED SURGERY	11 (4.8)	10 (4.3)
MAJOR PATHOLOGIC RESPONSE		
YES	90 (39.3)	33 (14.2)
NO	67 (29.3)	126 (54.3)
NOT EVALUABLE	11 (4.8)	9 (3.9)
NO SAMPLE AVAILABLE	61 (26.6)	64 (27.6)
NOT RECEIVED SURGERY	50 (21.8)	54 (23.3)
RECEIVED SURGERY	11 (4.8)	10 (4.3)
%PRIMARY TUMOR AREA WITH VIABLE TUMOR		
N	157	159
MEAN	25.5	52.7
MEDIAN	5.0	60.0
MIN, MAX	0, 100	0, 100
Q1, Q3	0.0, 43.0	20.0, 85.0
STANDARD DEVIATION	34.0	34.2
LYMPH NODES REGION:		
COMPLETE PATHOLOGIC RESPONSE		
YES	99 (43.2)	78 (33.6)
NO	48 (21.0)	69 (29.7)
NOT APPLICABLE	10 (4.4)	12 (5.2)
NOT EVALUABLE	11 (4.8)	9 (3.9)
NO SAMPLE AVAILABLE	61 (26.6)	64 (27.6)
NOT RECEIVED SURGERY	50 (21.8)	54 (23.3)
RECEIVED SURGERY	11 (4.8)	10 (4.3)
MAJOR PATHOLOGIC RESPONSE		
YES	105 (45.9)	81 (34.9)
NO	42 (18.3)	66 (28.4)
NOT APPLICABLE	10 (4.4)	12 (5.2)
NOT EVALUABLE	11 (4.8)	9 (3.9)
NO SAMPLE AVAILABLE	61 (26.6)	64 (27.6)

NOT RECEIVED SURGERY	50 (21.8)	54 (23.3)
RECEIVED SURGERY	11 (4.8)	10 (4.3)
%TUMOR AREA WITH VIABLE TUMOR CELLS		
N	86	80
MEAN	37.6	63.0
MEDIAN	10.0	75.0
MIN, MAX	0, 100	0, 100
Q1, Q3	0.0, 95.0	30.0, 98.0
STANDARD DEVIATION	43.3	37.8

Subjects without an evaluable sample or no sample available were counted as non-responders.

(1) Confidence interval based on the Clopper and Pearson method.

(2) Strata adjusted difference based on Cochran-Mantel-Haenszel (CMH) method of weighting.

(3) Stratified by tumour PD-L1 (>=1% vs <1%/not evaluable/indeterminate), disease stage (II vs III), Histology (squamous vs non-squamous) as entered into the IRT.

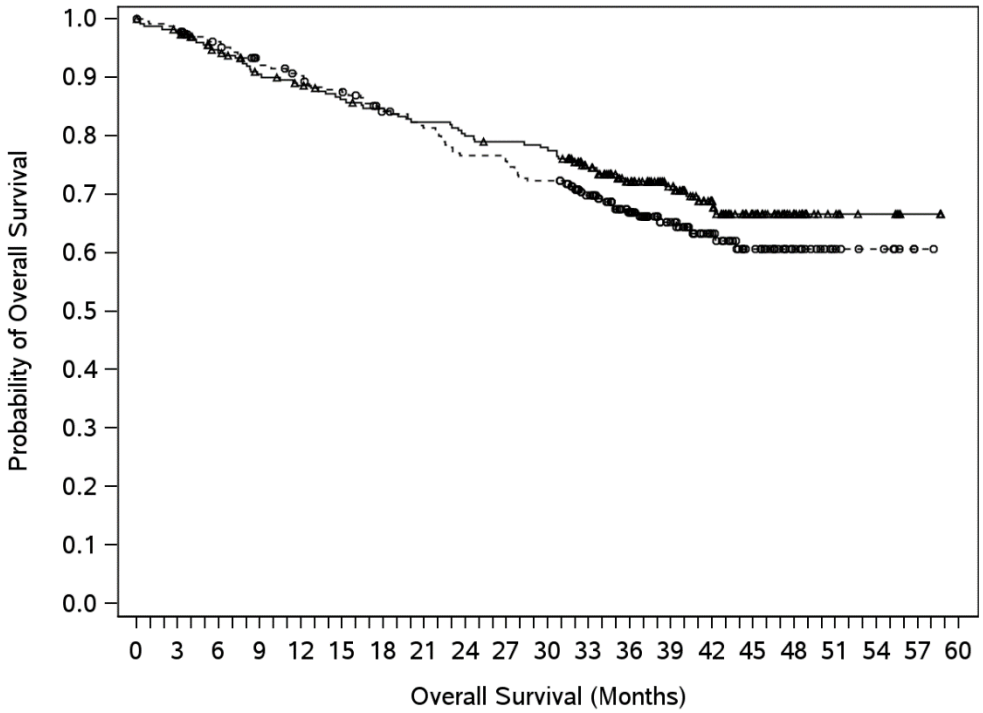
(4) Strata adjusted odds ratio using Mantel-Haenszel method.

Overall survival

At OS IA (DCO: 11-Nov-2024; DBL: 16-Dec-2024), the OS HR = 0.85 (97.63% CI: 0.58, 1.25; 95% CI: 0.61, 1.18), p = 0.33030. This OS IA was conducted at 80% information fraction (140 events). Minimum follow-up was 31.3 months, and median follow-up was 41.0 months.

Median OS was not reached in either arm.

Figure 6. Kaplan-Meier Plot of Overall Survival - All Randomized Subjects in the Global Population



Number of Subjects at Risk

Arm A: Nivo+Chemo/Nivo

229 222 206 193 187 180 176 171 166 163 161 138 114 91 66 43 23 10 6 2 0

Arm B: Pla+Chemo/Pla

232 228 216 203 197 190 178 171 161 159 152 131 103 72 52 35 20 10 7 1 0

Arm A: Nivo+Chemo/Nivo (events: 64/229), median and 95% CI: N.A.

Arm B: Pla+Chemo/Pla (events: 76/232), median and 95% CI: N.A.

Arm A vs. Arm B - hazard ratio (97.63% CI): 0.85 (0.58, 1.25), p-value: 0.33030

Statistical model for hazard ratio: Stratified Cox proportional hazard model.

Symbols represent censored observations.

Table 23. Overall Survival Rates - All Randomized Subjects in the Global Population

Overall Survival Rate (95% CI)	Arm A: Nivolumab + Chemo / Nivolumab / Placebo N = 229	Arm B: Placebo + Chemo N = 232
6-MONTH	94.2 (90.2, 96.6)	96.1 (92.6, 97.9)
12-MONTH	88.6 (83.6, 92.1)	90.2 (85.5, 93.4)
18-MONTH	84.8 (79.2, 88.9)	84.2 (78.7, 88.4)
24-MONTH	79.9 (73.9, 84.7)	76.6 (70.3, 81.7)
30-MONTH	78.0 (71.8, 83.0)	72.3 (65.8, 77.8)

Based on Kaplan-Meier estimates. DCO: 11-Nov-2024

Subsequent cancer therapies are described in Table 17.

Table 24. Status of censored subjects, Overall Survival. All randomized subjects in Global Population.

	Number of Subjects (%)	
	Arm A: Nivo + Chemo / Nivo N = 229	Arm B: Placebo + Chemo / Placebo N = 232
NUMBER OF DEATHS (%)	64 (27.9)	76 (32.8)
NUMBER OF SUBJECTS CENSORED (%)	165 (72.1)	156 (67.2)
STATUS OF CENSORED SUBJECTS (%)		
STILL ON-TREATMENT	4 (1.7)	0
NOT PROGRESSED/RECURRED	3 (1.3)	0
PROGRESSED/RECURRED (1)	1 (0.4)	0
IN FOLLOW-UP	142 (62.0)	130 (56.0)
OFF STUDY	19 (8.3)	26 (11.2)
LOST TO FOLLOW-UP	4 (1.7)	2 (0.9)
SUBJECT WITHDREW CONSENT	7 (3.1)	8 (3.4)
OTHER	8 (3.5)	16 (6.9)

(1) Event Free Survival Event per BICR secondary definition
DCO: 11-Nov-2024

Exploratory endpoints

ORR prior to surgery

Table 25. Best Overall Response - All Randomized Subjects in the Global Population

	Number of Subjects (%)	
	Arm A Nivolumab + Chemo/Nivolumab N = 229	Arm B Placebo + Chemo/Placebo N = 232
BEST OVERALL RESPONSE		
COMPLETE RESPONSE (CR)	7 (3.1)	6 (2.6)
PARTIAL RESPONSE (PR)	126 (55.0)	93 (40.1)
STABLE DISEASE (SD)	73 (31.9)	107 (46.1)
PROGRESSIVE DISEASE (PD)	9 (3.9)	13 (5.6)
UNABLE TO DETERMINE (UTD)	14 (6.1)	13 (5.6)
OBJECTIVE RESPONSE RATE (1)	133/229 (58.1%)	99/232 (42.7%)
(95% CI)	(51.4, 64.5)	(36.2, 49.3)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2) (3)	15.4%	
(95% CI)	(6.5, 24.4)	
ESTIMATE OF ODDS RATIO (3) (4)	1.90	
(95% CI)	(1.30, 2.76)	

Per RECIST 1.1 unconfirmed response prior to definitive surgery.

For subjects who did not undergo surgery, best overall response is defined as first protocol defined tumour response.

(1) CR+PR, confidence interval based on the Clopper and Pearson method.

(2) Strata adjusted difference based on Cochran-Mantel-Haenszel (CMH) method of weighting.

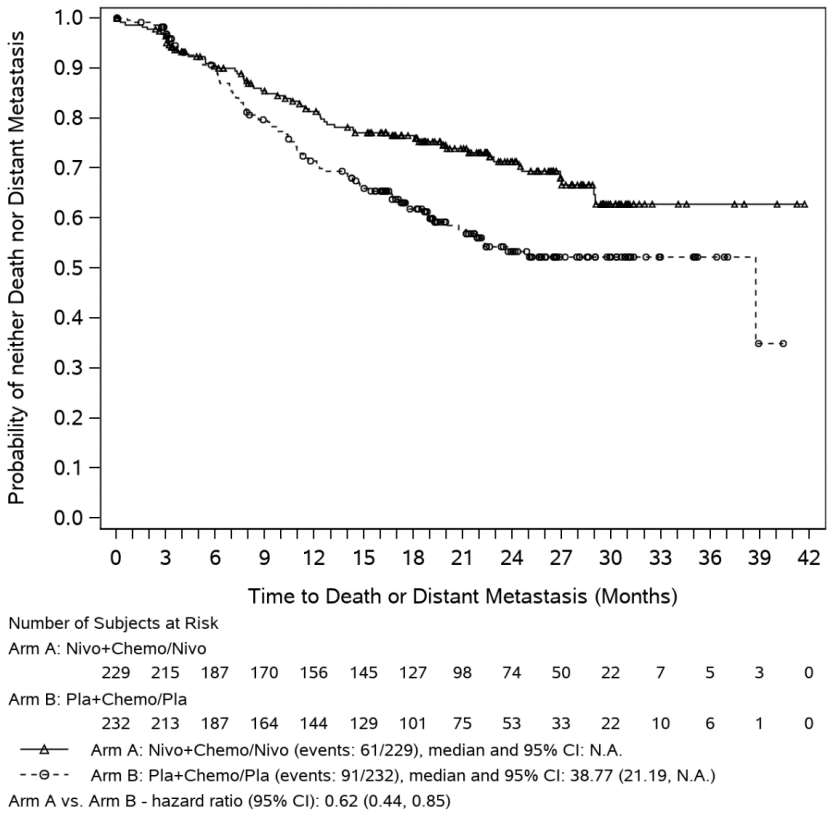
(3) Stratified by tumour PD-L1 (>=1% vs <1%/not evaluable/indeterminate), disease stage (II vs III), histology (squamous vs non-squamous) as entered into the IRT.

(4) Strata adjusted odds ratio using Mantel-Haenszel method.

DCO 26-Jul-2023

Time to death or distant metastasis (TTDM) by investigator

Figure 7. Time to Death or Distant Metastasis per Investigator - All Randomized Subjects in the Global Population



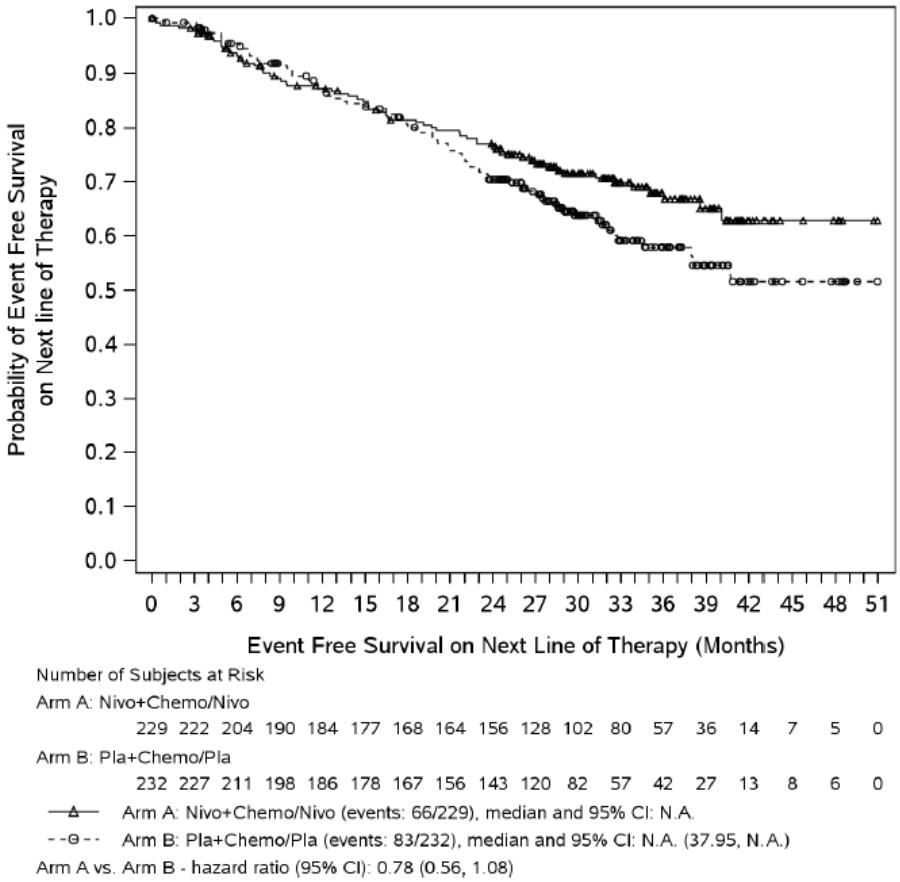
Symbols represent censored observations.

Statistical model for hazard ratio: stratified Cox proportional hazard model

DCO 26-Jul-2023Updated results (DCO 22-Mar-2024) were consistent (HR 0.62; 95% CI: 0.46, 0.85). Median TTDM was not reached in the nivo+chemo/nivolumab arm and was of 32.33 (95% CI: 22.21, NA) months in the placebo+chemo/placebo arm.

Event-Free Survival on next line of therapy (EFS2) per investigator

Figure 8. Event-Free Survival on Next Line of Therapy (EFS2) - All Randomized Subjects in the Global Population



Statistical model for hazard ratio: Stratified Cox proportional hazard model. Symbols represent censored observations.

DCO 22-Mar-2024

Exploratory endpoints: Patient Reported Outcomes (PRO)

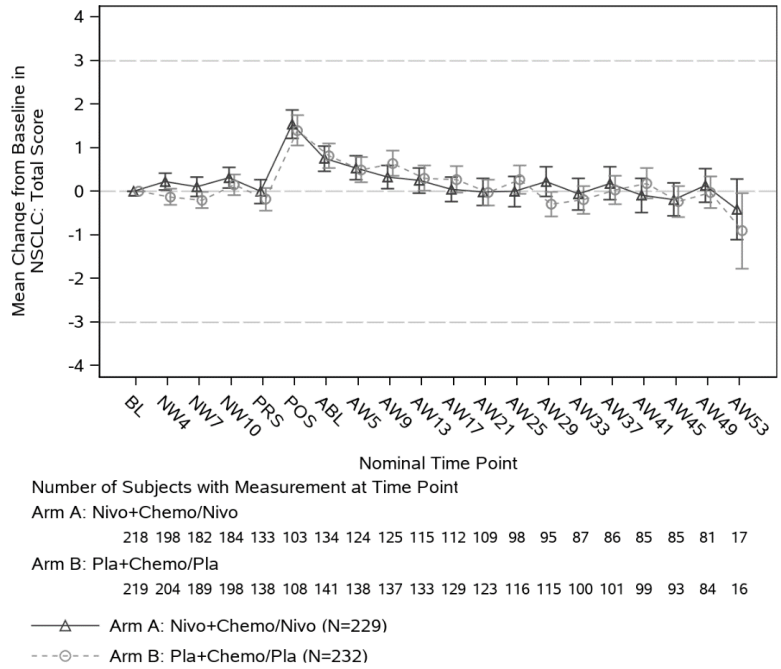
PRO Questionnaire Compliance

The NSCLC-SAQ questionnaire completion rates reported in all randomized subjects were ≥ 95% at baseline and ≥ 88% at most subsequent on-treatment assessments with sufficient data (≥ 10 subjects), except for the pre-surgical and post-surgical visits where the completion rates were lower (pre-surgery: 75.1% - 78.6%; post-surgery: 58.6% - 61.0%). During the treatment period, ≥ 10 subjects were eligible to respond at all timepoints up to Adjuvant Week 53 in both treatment arms.

PROs are presented per the EFS IA DCO (26-Jul-2023)

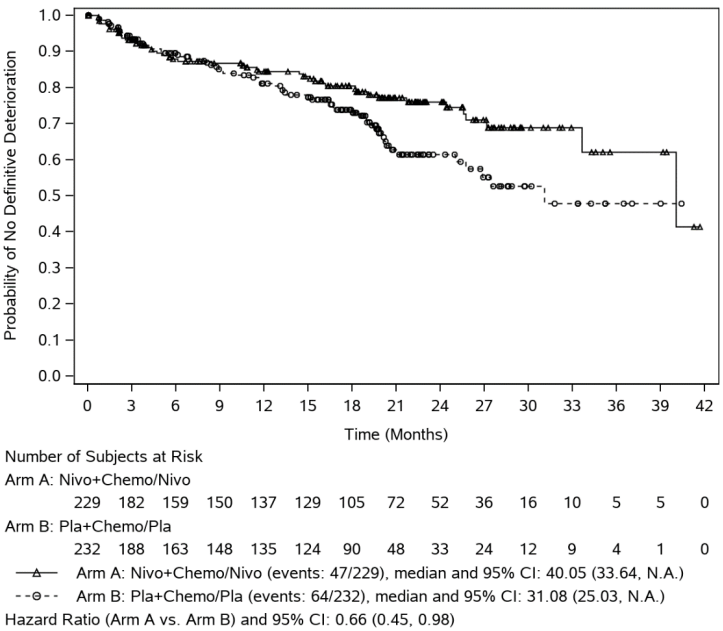
NSCLC - SAQ

Figure 9. Mean Changes from Baseline in NSCLC-SAQ - All Randomized Subjects in the Global Population



Error bars represent standard error for the mean.
Horizontal reference line indicates minimum important difference (MID), considered a change of ≥ 3 points from baseline.
Only time points where data available for ≥ 5 subjects in each treatment group are plotted.
The baseline is defined as last assessments performed prior to neoadjuvant C1D1 treatment.
Abbreviations: BL=baseline; NWx=neoadjuvant week x; PRS=pre surgery; POS=post surgery; AWx=adjuvant week x.

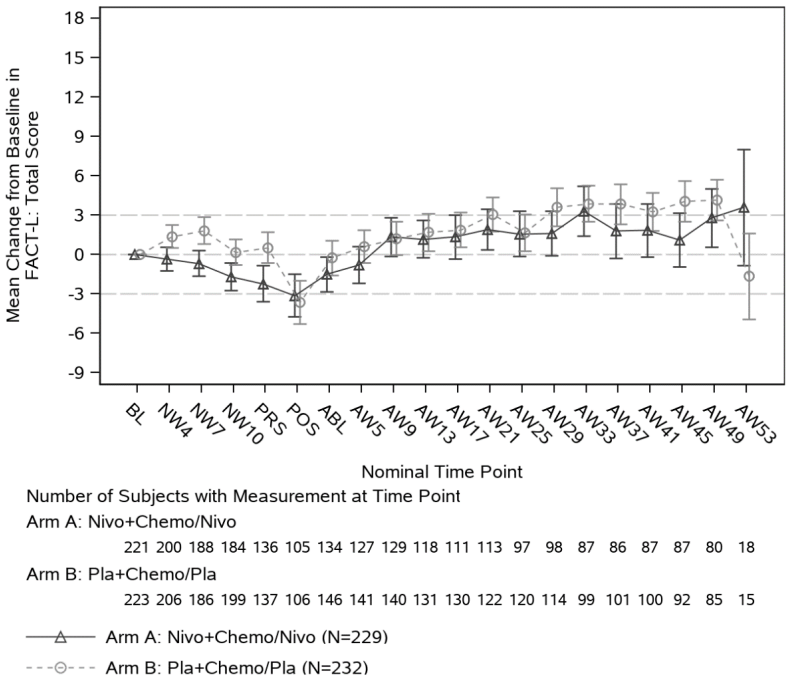
Figure 10. Time to Definitive Deterioration in NSCLC-SAQ: All Randomized Subjects in the Global Population



Symbols represent censored observations.
Stratified Cox proportional hazard model with baseline PRO score as a covariate
The baseline is defined as last assessments performed prior to neoadjuvant C1D1 treatment.

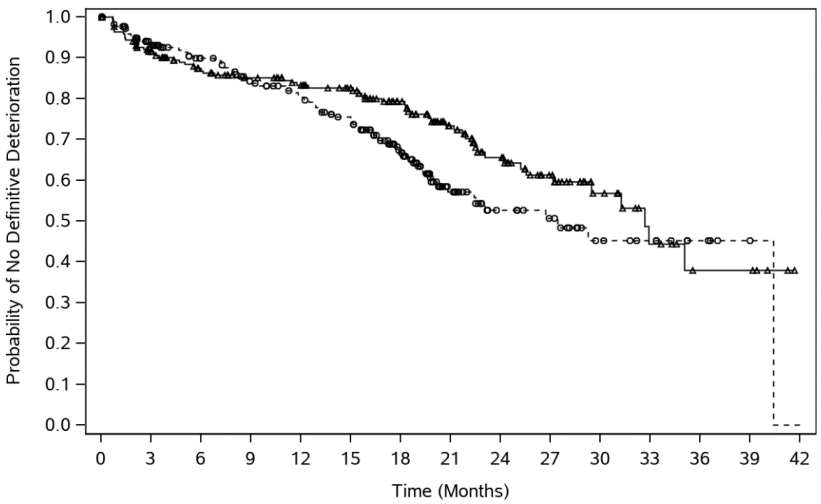
FACT-L

Figure 11. Mean Changes from Baseline in FACT-L Total Score - All Randomized Subjects in the Global Population



Error bars represent standard error for the mean.
Horizontal reference line indicates minimum important difference (MID), considered a change of >= 3 points from baseline.
Only time points where data available for >=5 subjects in each treatment group are plotted.
The baseline is defined as last assessments performed prior to neoadjuvant C1D1 treatment.
BL=baseline; NWx=neoadjuvant week x; PRS=pre surgery; POS=post-surgery; AWx=adjuvant week x.

Figure 12. Time to Definitive Deterioration in FACT LCSS - All Randomized Subjects in the Global Population



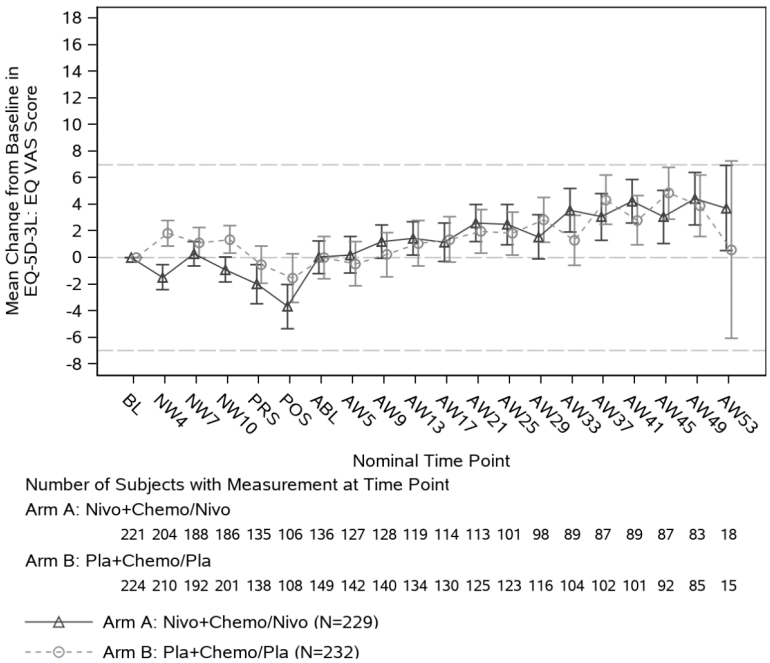
Symbols represent censored observations.
Stratified Cox proportional hazard model with baseline PRO score as a covariate

The baseline is defined as last assessments performed prior to neoadjuvant C1D1 treatment.

EQ-5D-3L

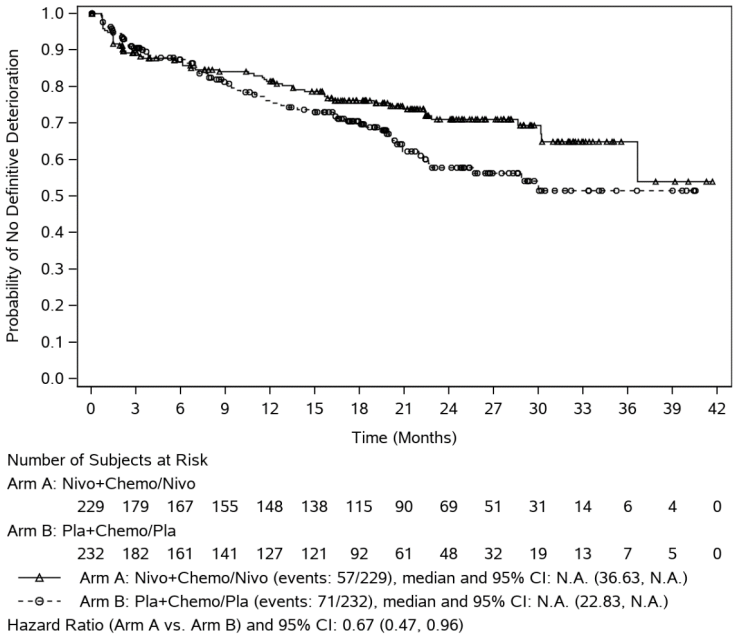
- EQ-5D-3L VAS

Figure 13. Mean Changes from Baseline in EQ-5D-3L VAS Score (Overall Self-Rated Health Status) - All Treated Subjects in the Global Population



Error bars represent standard error for the mean.
Horizontal reference line indicates minimum important difference (MID), considered a change of >= 0.08 points from baseline.
Only time points where data available for >=5 subjects in each treatment group are plotted.
The baseline is defined as last assessments performed prior to neoadjuvant C1D1 treatment.
BL=baseline; NWx=neoadjuvant week x; PRS=pre surgery; POS=post surgery; AWx=adjuvant week x.

Figure 14. Time to Definitive Deterioration in EQ-5D-3L Visual Analogue Score (Overall Self-Rated Health Status) - All Randomized Subjects in the Global Population



Symbols represent censored observations.

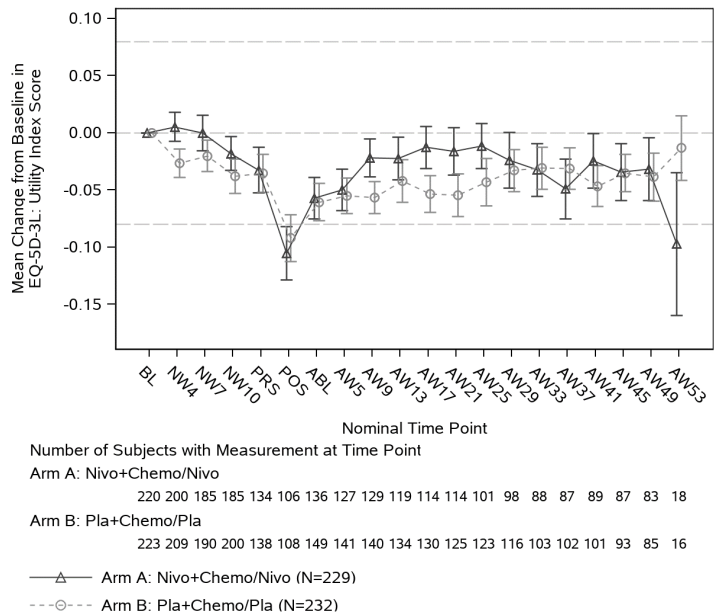
Stratified Cox proportional hazard model with baseline PRO score as a covariate

The baseline is defined as last assessments performed prior to neoadjuvant C1D1 treatment.

Definitive deterioration is defined as a change from baseline of 7 with no further improvement in score or any further data.

- EQ-5D-3L UI

Figure 15. Mean Changes from Baseline in EQ-5D-3L Utility Index Score (Overall Self-Rated Health Status) - All Treated Subjects in the Global Population



Error bars represent standard error for the mean.

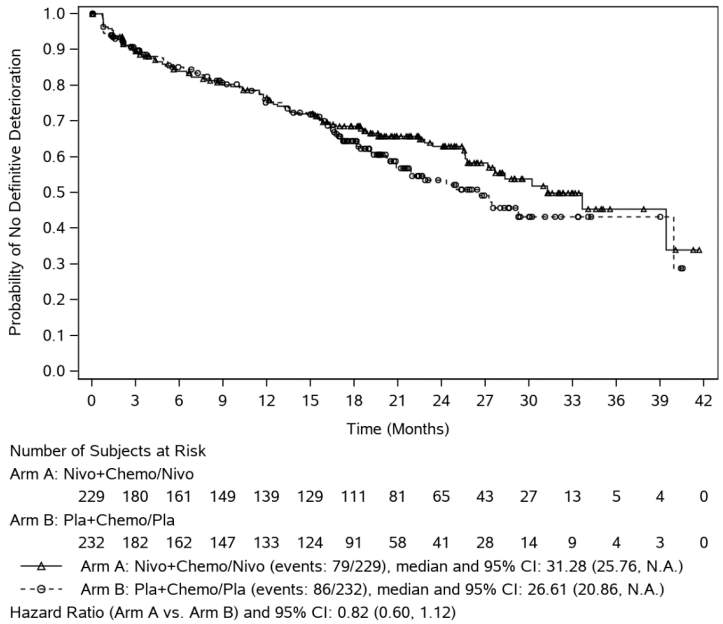
Horizontal reference line indicates minimum important difference (MID), considered a change of >= 0.08 points from baseline.

Only time points where data available for >=5 subjects in each treatment group are plotted.

The baseline is defined as last assessments performed prior to neoadjuvant C1D1 treatment.

BL=baseline; NWx=neoadjuvant week x; PRS=pre surgery; POS=post surgery; AWx=adjuvant week x.

Figure 16. Time to Definitive Deterioration in EQ-5D-3L Utility Index Score (Overall Self-Rated Health Status) - All Randomized Subjects in the Global Population



Symbols represent censored observations. Stratified Cox proportional hazard model with baseline PRO score as a covariate. The baseline is defined as last assessments performed prior to neoadjuvant C1D1 treatment.
Definitive deterioration is defined as a change from baseline of 0.08 with no further improvement in score or any further data.

Patient-Global Impression of Severity (PGI-S)

The proportions of subjects who reported each response level for the PGI-S were similar between treatment groups at most time points.

PROMIS Physical Function

At baseline, mean PROMIS Physical Function T-scores reported were similar in the nivolumab + chemo/nivolumab and placebo+chemo/placebo arms. Subjects in both arms had stable mean PROMIS Physical Function T-scores reported during the neoadjuvant treatment period followed by a worsening (decrease) at the post-surgical visit with subsequent improvements approaching baseline scores during the adjuvant treatment period.

After controlling for baseline score and relevant covariates, subjects in the nivo+chemo/nivolumab and placebo+chemo/placebo arms had a small worsening (decrease) in PROMIS Physical Function T-scores overall (during the neoadjuvant, surgical, and adjuvant periods). The change from baseline, LS mean (95% CI) was -1.84 (-2.67, -1.01) vs -2.41 (3.24, 1.58).

Ancillary analyses

Sensitivity analyses

Table 26. Sensitivity analyses – All Randomized Subjects in the Global Population

Sensitivity Analysis	Result HR (95% CI)
Primary Efficacy Endpoint: EFS per BICR (primary definition)[a]	**0.58 (0.43, 0.78)**
EFS per BICR using the secondary EFS definition[b]	0.61 (0.46, 0.81)

Sensitivity Analysis	Result HR (95% CI)
Accounting for missing tumour assessments prior to the EFS (per BICR) event; for subjects with 2 or more missed visits prior to the EFS event, EFS was censored at the last tumour assessment prior to the EFS event	0.57 (0.42, 0.76)
Using an unstratified Cox model (EFS per BICR)	0.59 (0.44, 0.79)
Excluding subjects from Russia (EFS per BICR)	0.55 (0.40, 0.75)
Multivariate Cox model of EFS per BICR adjusted for the following baseline factors: sex (male, female), ECOG PS (0, ≥ 1), race (Asian vs White), and smoking status (current/former vs never smoker) and stratified by tumour histology (SQ vs NSQ), disease stage (II vs III), and tumour PD-L1 status (≥ 1% vs < 1%/not evaluable /indeterminate). None of these baseline factors were significant prognostic variables in this model.	0.59 (0.44, 0.80)
EFS accounting for BICR progression prior to surgery	0.59 (0.44, 0.79)
EFS per BICR using interval censoring	0.59 (0.44, 0.79)

[a] The primary definition of EFS accounts for subsequent therapy by censoring at the last evaluable tumour assessment on or prior to the date of subsequent therapy (outside of the protocol-specified adjuvant therapy).

[b] The secondary definition of EFS does not apply censoring at subsequent anticancer therapy usage.

Subgroup analyses

EFS at primary analysis (DCO: 26-Jul-2023)

Figure 17. Treatment Effect on Event-Free Survival per BICR, Primary Definition in Predefined Subsets - All Randomized Subjects in the Global Population per patients demographics

		Arm A: Nivo+Chemo/Nivo		Arm B: Pla+Chemo/Pla		Unstratified
		N of Events	mEFS	N of Events	mEFS	Hazard Ratio (95% CI)
	N	(N of Subjects)	(95% CI)	(N of Subjects)	(95% CI)	Arm A vs. Arm B
Overall	461	76 (229)	N.A. (28.94, N.A.)	113 (232)	18.43 (13.63, 28.06)	0.59 (0.44, 0.79)
Age Categorization						
< 65	202	36 (102)	N.A. (24.41, N.A.)	52 (100)	16.72 (11.01, 28.19)	0.55 (0.36, 0.85)
>= 65 and < 75	228	37 (115)	30.23 (28.94, N.A.)	52 (113)	22.05 (12.16, N.A.)	0.66 (0.43, 1.01)
>= 75	31	3 (12)	N.A. (3.29, N.A.)	9 (19)	10.15 (6.87, N.A.)	0.35 (0.09, 1.31)
>= 65	259	40 (127)	N.A. (28.94, N.A.)	61 (132)	20.07 (11.20, N.A.)	0.61 (0.41, 0.91)
Sex						
Male	327	53 (167)	N.A. (28.94, N.A.)	78 (160)	16.72 (10.15, N.A.)	0.53 (0.37, 0.75)
Female	134	23 (62)	30.23 (19.68, N.A.)	35 (72)	18.76 (14.72, 35.06)	0.71 (0.41, 1.20)
Race						
White	330	56 (155)	30.23 (24.57, N.A.)	86 (175)	17.74 (13.63, 28.06)	0.68 (0.49, 0.96)
Black or African American	8	0 (4)	N.A.	2 (4)	7.20 (6.47, N.A.)	
Asian	116	20 (66)	N.A. (24.25, N.A.)	24 (50)	13.86 (8.08, N.A.)	0.47 (0.26, 0.85)
Other	7	0 (4)	N.A.	1 (3)	19.81 (N.A., N.A.)	
Region						
North America	44	11 (23)	30.23 (7.89, N.A.)	11 (21)	9.36 (6.24, 22.05)	0.59 (0.25, 1.38)
Europe	250	37 (123)	N.A. (27.01, N.A.)	58 (127)	23.72 (15.08, N.A.)	0.61 (0.40, 0.92)
Asia	115	20 (65)	N.A. (24.25, N.A.)	24 (50)	13.86 (8.08, N.A.)	0.47 (0.26, 0.86)
Rest of World	52	8 (18)	N.A. (4.37, N.A.)	20 (34)	16.36 (8.08, N.A.)	0.84 (0.37, 1.92)
ECOG Performance Status						
0	288	46 (147)	N.A. (27.01, N.A.)	68 (141)	20.07 (12.58, N.A.)	0.57 (0.39, 0.83)
1	173	30 (82)	29.04 (22.60, N.A.)	45 (91)	17.28 (10.55, 35.06)	0.61 (0.39, 0.97)
Smoking Status						
Current/Former	417	67 (212)	N.A. (29.04, N.A.)	102 (205)	16.99 (11.37, 28.06)	0.54 (0.40, 0.74)
Never Smoked	44	9 (17)	19.68 (3.68, N.A.)	11 (27)	25.00 (13.86, N.A.)	1.32 (0.54, 3.20)

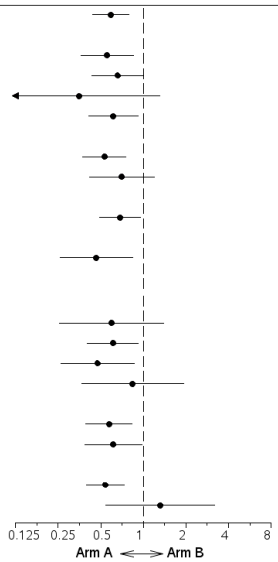


Figure 18. Treatment Effect on Event-Free Survival per BICR, Primary Definition in Predefined Subsets - All Randomized Subjects in the Global Population per disease characteristics

	N	Arm A: Nivo+Chemo/Nivo N of Events (N of Subjects)	Arm A: Nivo+Chemo/Nivo mEFS (95% CI)	Arm B: Pla+Chemo/Pla N of Events (N of Subjects)	Arm B: Pla+Chemo/Pla mEFS (95% CI)	Unstratified Hazard Ratio (95% CI) Arm A vs. Arm B
Disease Stage per CRF						
Stage <= II	162	22 (81)	N.A. (22.60, N.A.)	27 (81)	N.A. (24.18, N.A.)	0.81 (0.46, 1.43)
Stage >= III	299	54 (148)	30.23 (26.91, N.A.)	86 (151)	13.40 (9.79, 17.74)	0.51 (0.36, 0.72)
Disease Stage per IRT						
Stage <= II	161	22 (81)	N.A. (24.57, N.A.)	30 (80)	N.A. (17.28, N.A.)	0.67 (0.39, 1.16)
Stage >= III	300	54 (148)	30.23 (26.91, N.A.)	83 (152)	14.29 (10.15, 19.81)	0.55 (0.39, 0.78)
Baseline Histology per CRF						
Squamous	234	31 (116)	N.A.	56 (118)	16.99 (10.15, N.A.)	0.46 (0.30, 0.72)
Non-Squamous	227	45 (113)	28.94 (21.39, N.A.)	57 (114)	18.43 (13.60, 28.06)	0.72 (0.49, 1.07)
Baseline Histology per IRT						
Squamous	235	33 (117)	N.A.	57 (118)	16.36 (9.95, N.A.)	0.49 (0.32, 0.75)
Non-Squamous	226	43 (112)	29.04 (24.41, N.A.)	56 (114)	18.76 (13.63, 28.06)	0.70 (0.47, 1.04)
PD-L1 Status per CRF						
< 1%	186	34 (93)	29.04 (21.39, N.A.)	44 (93)	19.81 (13.86, N.A.)	0.73 (0.47, 1.15)
>= 1%	256	39 (128)	N.A. (28.94, N.A.)	63 (128)	15.80 (9.33, 35.06)	0.52 (0.35, 0.78)
1-49%	159	30 (83)	30.23 (20.01, N.A.)	33 (76)	28.06 (11.01, N.A.)	0.76 (0.46, 1.25)
>= 50%	97	9 (45)	N.A.	30 (52)	7.98 (6.28, 23.72)	0.26 (0.12, 0.55)
Not Evaluable/Indeterminate	19	3 (8)	N.A. (3.32, N.A.)	6 (11)	16.72 (8.18, N.A.)	
Type of Platinum Therapy						
Cisplatin	97	25 (55)	27.01 (21.29, N.A.)	24 (42)	15.80 (8.77, 28.06)	0.61 (0.35, 1.08)
Carboplatin	347	48 (167)	N.A. (29.04, N.A.)	87 (180)	17.28 (12.58, 35.06)	0.53 (0.37, 0.75)
Switching from Cis. to Carbo.	11	3 (5)	12.17 (2.63, N.A.)	2 (6)	N.A. (10.55, N.A.)	
Not Reported	6	0 (2)	N.A.	0 (4)	N.A.	

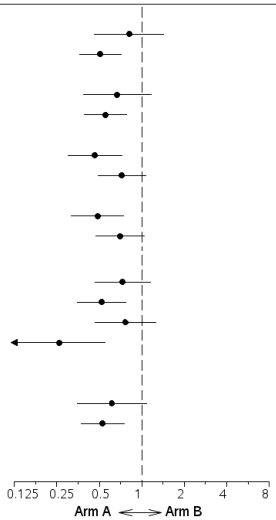
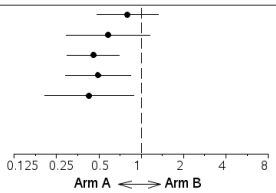


Figure 19. Treatment Effect on Event-Free Survival per BICR, Primary Definition in Predefined Subsets - All Randomized Subjects in the Global Population per nodal status

	N	Arm A: Nivo+Chemo/Nivo N of Events (N of Subjects)	Arm A: Nivo+Chemo/Nivo mEFS (95% CI)	Arm B: Pla+Chemo/Pla N of Events (N of Subjects)	Arm B: Pla+Chemo/Pla mEFS (95% CI)	Unstratified Hazard Ratio (95% CI) Arm A vs. Arm B
CN0	167	27 (80)	N.A. (24.25, N.A.)	35 (87)	N.A. (15.80, N.A.)	0.80 (0.48, 1.32)
CN1	108	14 (56)	N.A. (24.41, N.A.)	20 (52)	28.06 (16.99, N.A.)	0.58 (0.29, 1.16)
CN2	182	35 (91)	30.23 (26.91, N.A.)	56 (91)	10.02 (8.08, 15.08)	0.46 (0.30, 0.70)
Single Station	112	24 (59)	30.23 (18.23, N.A.)	32 (53)	9.95 (6.47, 18.43)	0.49 (0.29, 0.84)
Multistation	69	11 (31)	N.A. (13.24, N.A.)	24 (38)	10.02 (7.98, 18.76)	0.43 (0.21, 0.88)
Not Reported	1	0 (1)	N.A.	0 (0)		
CN3	4	0 (2)	N.A.	2 (2)	18.86 (2.66, N.A.)	



HR is not computed for subset category with less than 10 subjects per treatment group.

- EFS per BICR by stratification factor subgroups

Table 27. EFS per BICR by Stratification Factor Subgroups per CRF - All Randomized Subjects in the Global Population

Stratification Factor Subgroups	HR (95% CI)[a,b]
Disease Stage at Study Entry	
II	0.81 (0.46, 1.43)
III	0.51 (0.36, 0.72)
PD-L1 Status	
< 1%	0.73 (0.47, 1.15)
≥ 1%	0.52 (0.35, 0.78)
Tumour Histology	
SQ	0.46 (0.30, 0.72)
NSQ	0.72 (0.49, 1.07)

[a] HR (95% CI) of nivo+chemo/nivolumab over placebo+chemo/placebo.

[b] Statistical model for hazard ratio: unstratified Cox proportional hazard model.

- EFS per BICR by pCR and MPR status

Table 28. Comparison Across Treatment Arms of Event-Free Survival per BICR by pCR and MPR Status: All Randomized Subjects in the Global Population

Median (months) EFS and 95% CI		Median (months) EFS and 95% CI	
Arm A Nivo+Chemo/Nivo	**Arm B Placebo+Chemo/Placebo**	**Arm A Nivo+Chemo/Nivo**	**Arm B Placebo+Chemo/Placebo**
With pCR		**No pCR**	
NA (NA, NA)	NA (20.07, NA)	27.01 (19.68, NA)	16.36 (11.37, 28.06)
HR = 0.33 (95% CI: 0.08, 1.37)		HR = 0.79 (95% CI: 0.58, 1.06)	
With MPR		**No MPR**	
NA (NA, NA)	35.06 (22.05, NA)	24.25 (14.52, 30.23)	14.72 (10.81, 19.81)
HR = 0.40 (95% CI: 0.16, 0.99)		HR = 0.85 (95% CI: 0.62, 1.15)	

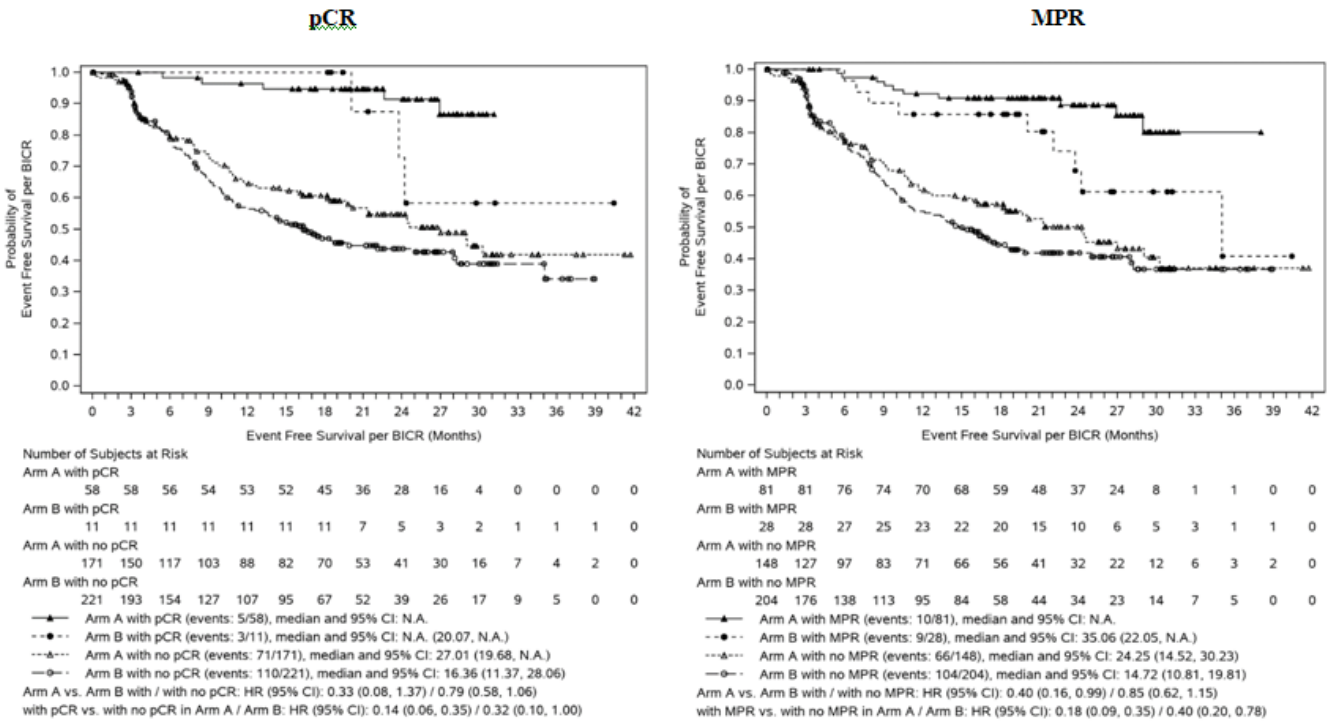
Statistical model for hazard ratio: Unstratified Cox proportional hazards model.

Table 29. Comparison Within Each Treatment Arm of Event-Free Survival per BICR by pCR and MPR Status: All Randomized Subjects in the Global Population

Median (months) EFS and 95% CI		Median (months) EFS and 95% CI	
Arm A Nivo+Chemo/Nivo	**Arm A Nivo+Chemo/Nivo**	**Arm B Placebo+Chemo/Placebo**	**Arm B Placebo+Chemo/Placebo**
pCR	**No pCR**	**pCR**	**No pCR**
NA (NA, NA)	27.01 (19.68, NA)	NA (20.07, NA)	16.36 (11.37, 28.06)
HR = 0.14 (95% CI: 0.06, 0.35)		HR = 0.32 (95% CI: 0.10, 1.00)	
MPR	**No MPR**	**MPR**	**No MPR**
NA (NA, NA)	24.25 (14.52, 30.23)	35.06 (22.05, NA)	14.72 (10.81, 19.81)
HR = 0.18 (95% CI: 0.09, 0.35)		HR = 0.40 (95% CI: 0.20, 0.78)	

Statistical model for hazard ratio: Unstratified Cox proportional hazards model.

Figure 20. EFS per BICR, Primary Definition From Randomization by pCR and MPR Status - All Randomized Subjects in the Global Population with pCR or MPR Status Available



Statistical model for hazard ratio: Unstratified Cox proportional hazards model.
Symbols represent censored observations.

- Updated EFS analysis (DCO: 11-Nov-2024)

Table 30. EFS per BICR by Stratification Factors, pCR Status, Surgery Received, and Adjuvant Therapy Received - All Randomized Subjects in the Global Population (DCO: 11-Nov-2024)

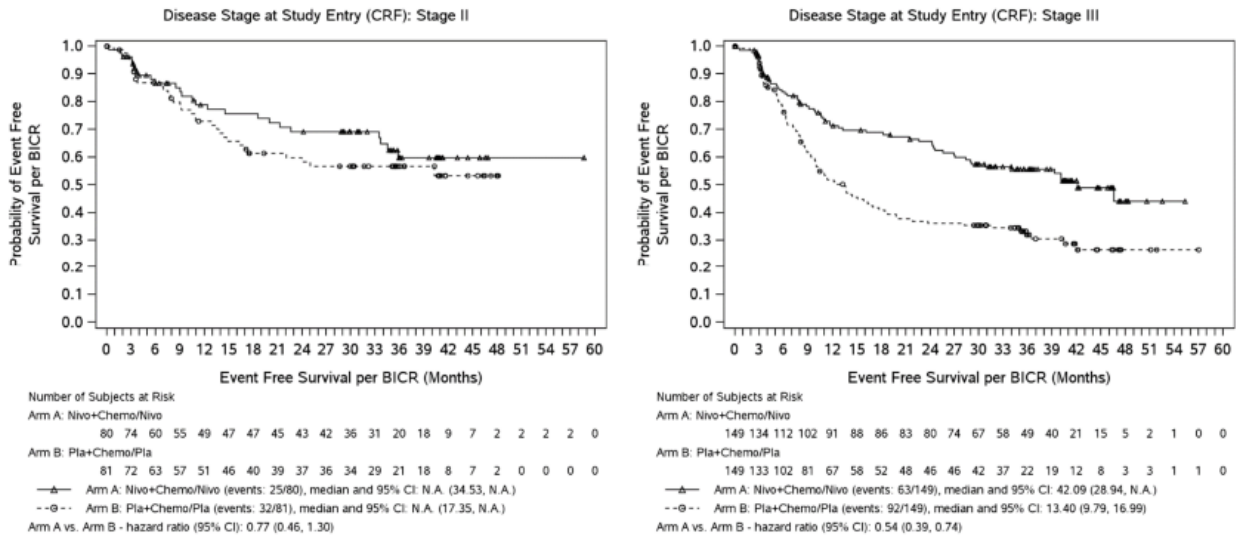
Subgroups	Number of Subjects		Nivo+Chemo/Nivo vs Placebo+Chemo/Placebo EFS HR (95% CI)[a]
	Nivo+Chemo/ Nivo Events/N subj	Placebo+Chemo/ Placebo Events/N subj	
All Randomized	88/229	124/232	0.61 (0.46, 0.80)
Stratification Factors[b]			
Disease Stage at Study Entry			
II	25/80	32/81	0.77 (0.46, 1.30)
III	63/149	92/149	0.54 (0.39, 0.74)
Tumour Histology			
SQ	39/116	59/118	0.53 (0.35, 0.80)
NSQ	49/113	65/114	0.69 (0.48, 1.00)
PD-L1 Status			
< 1%	38/93	47/93	0.79 (0.52, 1.21)
≥ 1%	47/128	70/128	0.53 (0.36, 0.76)
1%-49%	35/83	38/76	0.74 (0.47, 1.17)

Subgroups	Number of Subjects		Nivo+Chemo/Nivo vs Placebo+Chemo/Placebo EFS HR (95% CI)[a]
	Nivo+Chemo/ Nivo Events/N subj	Placebo+Chemo/ Placebo Events/N subj	
≥ 50%	12/45	32/52	0.30 (0.15, 0.59)
pCR Status			
Achieved pCR	9/58	2/11	0.89 (0.19, 4.12)
Did not achieve pCR	79/171	122/221	0.79 (0.59, 1.05)
Surgery Received			
Yes	57/178	90/178	0.52 (0.38, 0.73)
No	31/51	34/54	0.67 (0.41, 1.10)
Adjuvant Therapy Received			
Yes	40/142	72/152	0.49 (0.33, 0.72)
No	48/87	52/80	0.56 (0.38, 0.84)

[a] Statistical model for hazard ratio: unstratified Cox proportional hazard model.

[b] Subgroups defined based on CRF (disease stage, tumour histology) or clinical database (PD-L1)

Figure 21. Updated Event-Free Survival per BICR, Primary Definition by Disease Stage at Study Entry - All Randomized Subjects in the Global Population (DCO: 11-Nov-2024)



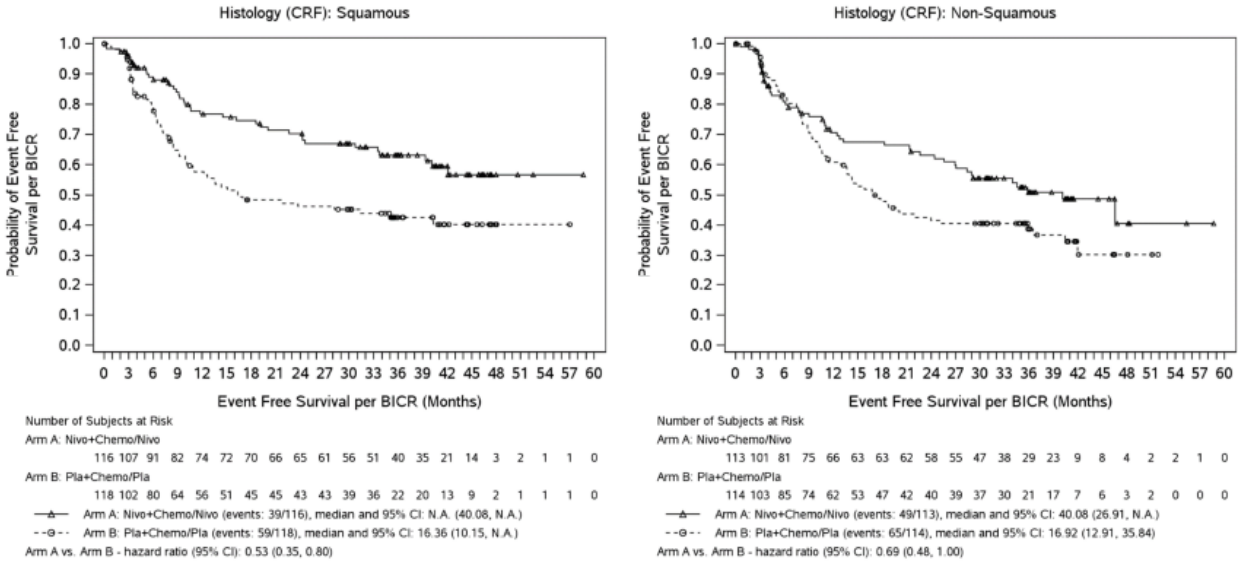
Statistical model for hazard ratio: Unstratified Cox proportional hazard model.

Symbols represent censored observations.

Subgroups defined based on disease stage at study entry per CRF. Subjects with disease stage other than II, III are excluded

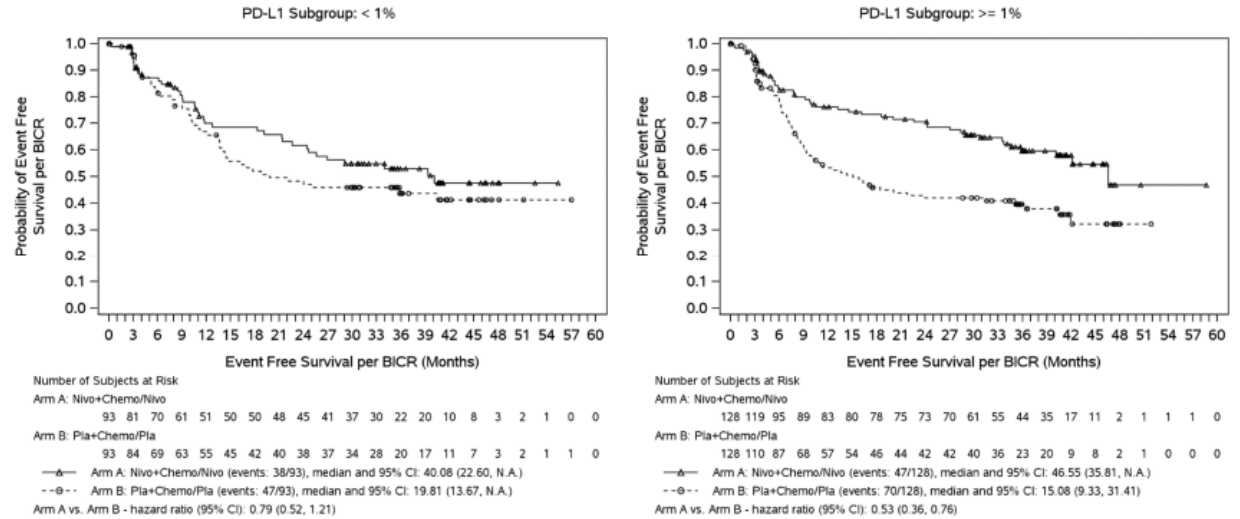
Source: Figure 14.2.1.6.2 in Attachment Q1

Figure 22. Updated Event-Free Survival per BICR, Primary Definition by Histology - All Randomized Subjects in the Global Population (DCO: 11-Nov-2024)



Statistical model for hazard ratio: Unstratified Cox proportional hazard model.
Symbols represent censored observations.
Subgroups defined based on histology at study entry per CRF.
Source: Figure 14.2.1.6.4 in Attachment Q1

Figure 23. Updated Event-Free Survival per BICR, Primary Definition by Baseline Tumour PD-L1 (< 1%, ≥1%) - All Randomized Subjects in the Global Population (DCO: 11-Nov-2024)



Statistical model for hazard ratio: Unstratified Cox proportional hazard model.
Symbols represent censored observations.
Subgroups defined based on baseline PD-L1 expression level recorded on clinical database.
Source: Figure 14.2.1.6.1 in Attachment Q1

Efficacy by baseline tumour PD-L1 expression (DCO: 26 July 2023)

Table 31. Efficacy by Baseline Tumour PD-L1 Level - All Randomized Subjects in the Global Population

	PD-L1 < 1%		PD-L1 ≥ 1%	
	Arm A Nivo+Chemo/Nivo N = 93	Arm B PBO+Chemo/ PBO N = 93	Arm A Nivo+Chemo/Nivo N = 128	Arm B PBO+Chemo/ PBO N = 128
EFS (per BICR, Primary definition)				
Events, n	34	44	39	63
Median (mo) [a]	29.04	19.81	NA	15.80
(95% CI)	(21.39, NA)	(13.86, NA)	(28.94, NA)	(9.33, 35.06)
HR (95% CI)[b]	0.73 (0.47, 1.15)		0.52 (0.35, 0.78)	
pCR per BIPR				
Rate (95% CI)	12.9 (6.8, 21.5)	4.3 (1.2, 10.6)	35.2 (26.9, 44.1)	4.7 (1.7, 9.9)
Diff (95% CI)[c]	8.6 (0.4, 17.3)		30.5 (21.2, 39.4)	
MPR per BIPR				
Rate (95% CI)	21.5 (13.7, 31.2)	9.7 (4.5, 17.6)	45.3 (36.5, 54.3)	13.3 (7.9, 20.4)
Diff (95% CI)[c]	11.8 (1.3, 22.2)		32.0 (21.2, 41.9)	
ORR per BICR[c]				
Rate (95% CI)	53.8 (43.1, 64.2)	43.0 (32.8, 53.7)	60.9 (51.9, 69.4)	43.8 (35.0, 52.8)
Diff (95% CI)[c]	10.8 (-3.5, 24.4)		17.2 (5.0, 28.7)	

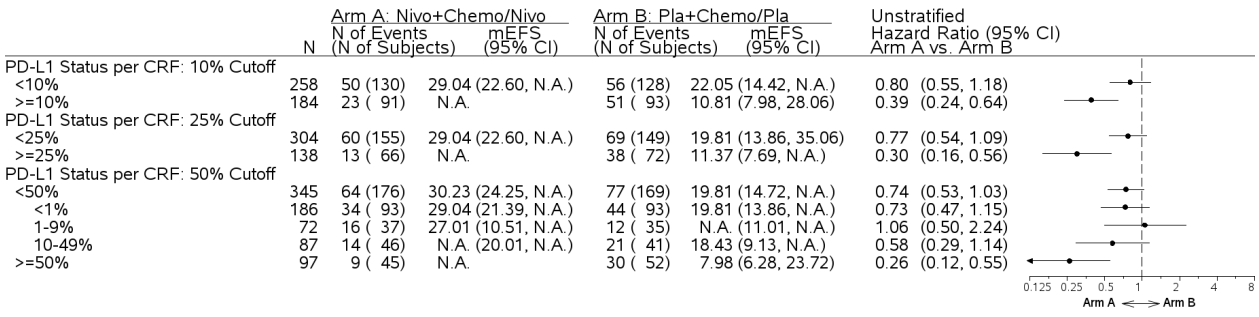
[a] Based on Kaplan-Meier estimates.

[b] Unstratified Cox proportional hazards model.

[c] Unweighted difference was calculated using Newcombe method.

[d] In subjects with measurable disease. Confidence interval based on the Clopper and Pearson method.

Figure 24. Treatment Effect on Event Free Survival per BICR, Primary Definition in PD-L1 Subsets - All Randomized Subjects in Global Population with Quantifiable PD-L1 Expression



HR is not computed for subset category with less than 10 subjects per treatment group.

OS subgroup analyses at OS interim analysis (DCO: 11-Nov-2024)

Table 32. Overall Survival by Stratification Factors All Randomized Subjects in the Global Population

Subgroups	Number of Subjects		Nivo+Chemo/Nivolumab vs Placebo+Chemo/Placebo OS HR (95% CI)[a]
	Nivo+Chemo/ Nivolumab Events/N subj	Placebo+Chemo/ Placebo Events/N subj	
All Randomized	64/229	76/232	0.85 (0.61, 1.18)
Stratification Factors[b]			
Disease Stage at Study Entry			
II	18/80	19/81	0.93 (0.49, 1.78)
III	46/149	55/149	0.82 (0.56, 1.22)
Tumour Histology			
SQ	32/116	40/118	0.73 (0.46, 1.16)
NSQ	32/113	36/114	0.94 (0.59, 1.52)
PD-L1 Status			
< 1%	32/93	29/93	1.19 (0.72, 1.97)
≥ 1%	31/128	46/128	0.61 (0.39, 0.97)
1%-49%	20/83	26/76	0.68 (0.38, 1.22)
≥ 50%	11/45	20/52	0.52 (0.25, 1.10)

[a] Statistical model for hazard ratio: unstratified Cox proportional hazard model.

[b] Subgroups defined based on CRF (disease stage, tumour histology) or clinical database (PD-L1)

- PD-L1 subgroups

Figure 25. Kaplan-Meier Plot of Overall Survival - PD-L1 Subgroup < 1%

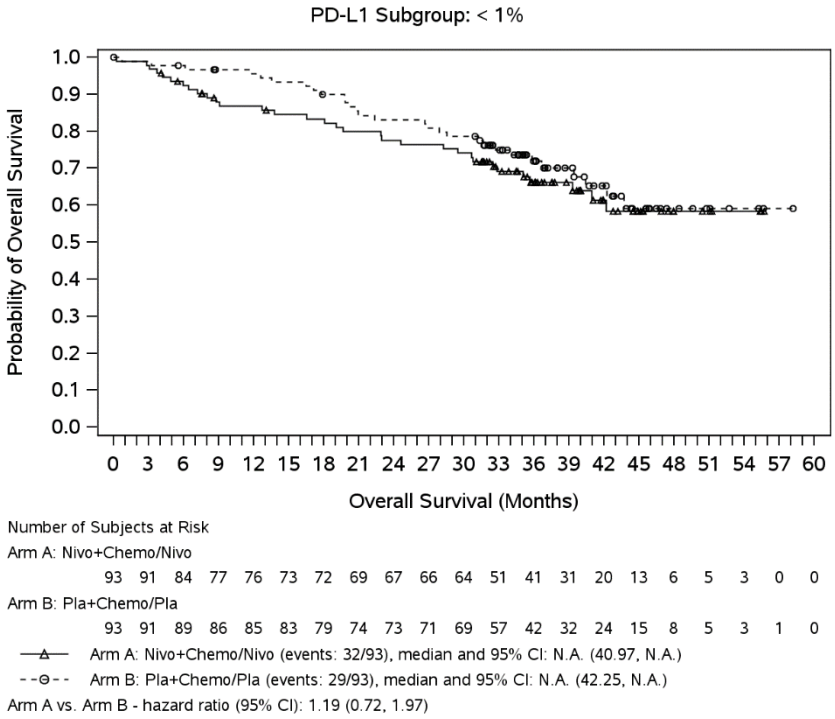
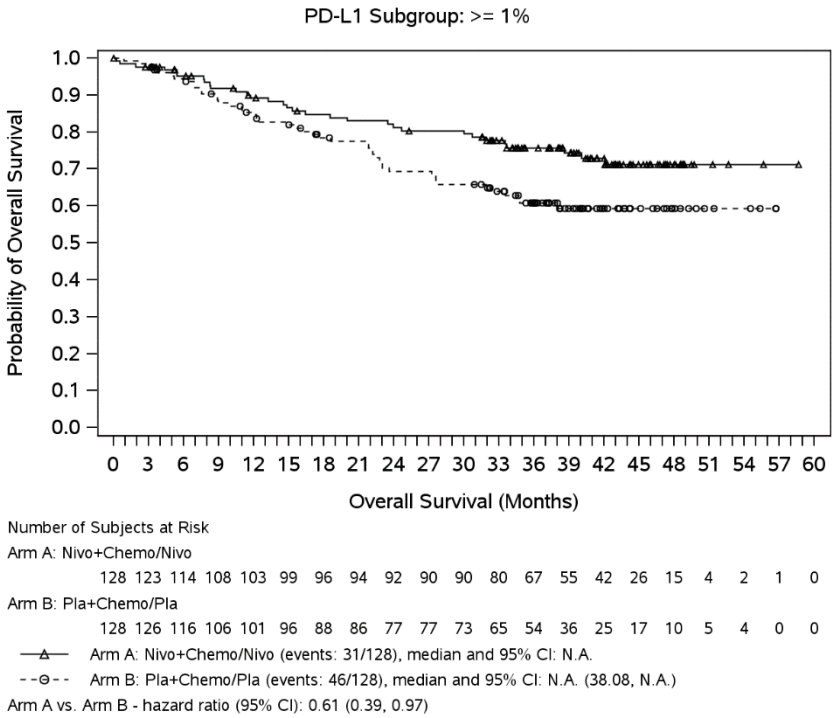


Figure 26. Kaplan-Meier Plot of Overall Survival - PD-L1 Subgroup ≥ 1%



Statistical model for hazard ratio: Unstratified Cox proportional hazard model.

Symbols represent censored observations.

Subgroups defined based on baseline PD-L1 expression level recorded on clinical database.

Efficacy by ctDNA clearance

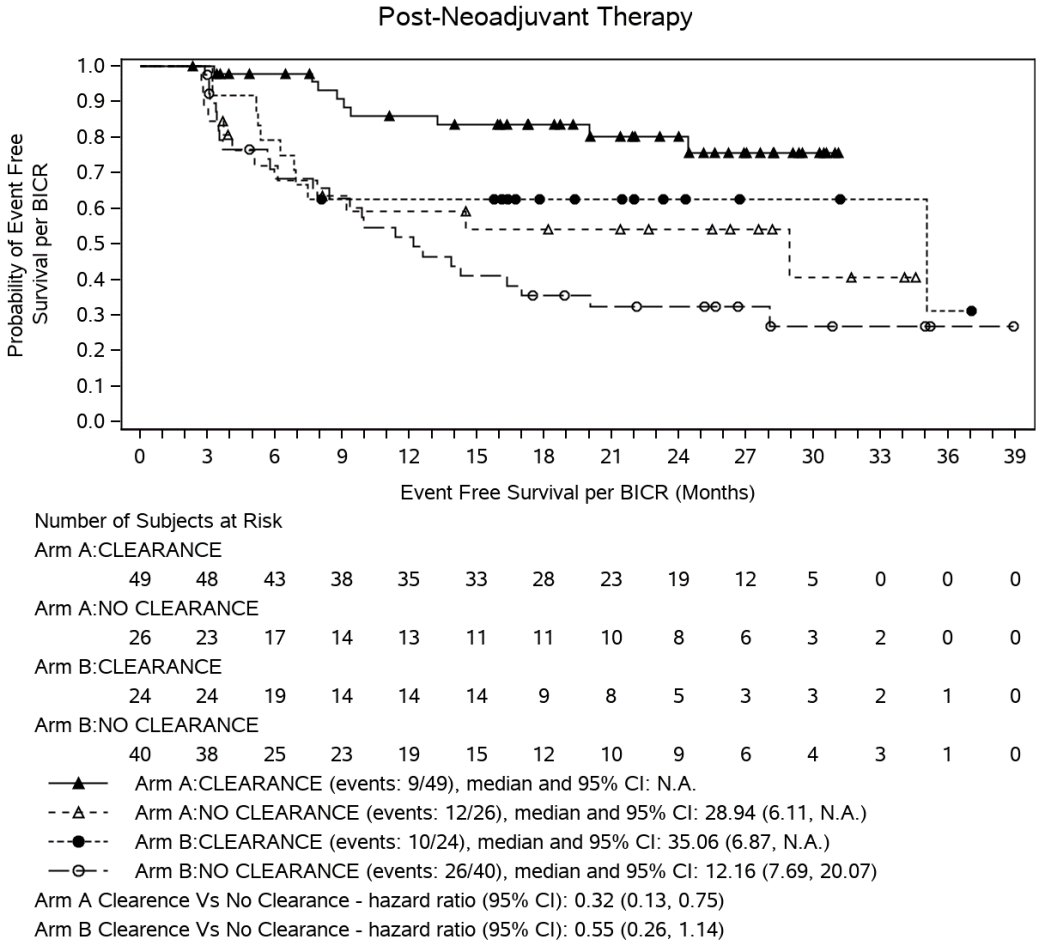
Table 33. Efficacy by ctDNA Clearance at Post-Neoadjuvant Therapy- All Randomized ctDNA Clearance Evaluable Subjects

	ctDNA Clearance		No ctDNA Clearance	
	Arm A Nivo+Chemo /Nivo N = 49	Arm B PBO+Chemo/ PBO N = 24	Arm A Nivo+Chemo /Nivo N = 26	Arm B PBO+Chemo/ PBO N = 40
EFS[a]				
Events, n (%)	9 (18.4)	10 (41.7)	12 (46.2)	26 (65.0)
Median (95% CI)	Not Reached	35.06 (6.87, NA)	28.94 (6.11, NA)	12.16 (7.69, 20.07)
pCR				
Responders, n (%)	24 (49.0)	3 (12.5)	0	1 (2.5)
95% CI	(34.4, 63.7)	(2.7, 32.4)	(0.0, 13.2)	(0.1, 13.2)
MPR				
Responders, n (%)	27 (55.1)	6 (25.1)	2 (7.7)	1 (2.5)
95% CI	(40.2, 69.3)	(9.8, 46.7)	(0.9, 25.1)	(0.1, 13.2)

[a] In the **nivo+chemo/nivolumab arm**, HR = 0.32 (95% CI: 0.13, 0.75) for subjects with ctDNA clearance vs subjects without ctDNA clearance.

In the **placebo+chemo/placebo arm**, HR = 0.55 (95% CI: 0.26, 1.14) for subjects with ctDNA clearance vs subjects without ctDNA clearance.

Figure 27. Event Free Survival per BICR, by ctDNA Clearance Post-Neoadjuvant Therapy - All Randomized ctDNA Clearance Evaluable Subjects in Global Population



Symbols represent censored observations.
Statistical model for hazard ratio: Unstratified Cox proportional hazards model.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 34. Summary of Efficacy for trial CA20977T

Title: A Phase 3, Randomized, Double-Blind Study Of Neoadjuvant Chemotherapy Plus Nivolumab Versus Neoadjuvant Chemotherapy Plus Placebo, Followed By Surgical Resection And Adjuvant Treatment With Nivolumab Or Placebo For Participants With Resectable Stage II-IIIB Non-Small Cell Lung Cancer	
Study identifier	CA20977T
Design	CA20977T is a randomized, double-blind, Phase 3 study in subjects with resectable early-stage non-small cell lung cancer (NSCLC): Stage IIA (> 4 cm) to IIIB (T3N2 or T4N2). Subjects with N3 nodal disease were not eligible. Subjects with resectable T4 tumour size with Stage IIIA or IIIB disease should have been reviewed and approved for participation in the study by the multidisciplinary team (including surgeon, medical oncologist, and radiation oncologist).

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		20-Nov-2019 (first subject randomized) to 26-Jul-2023 (DCO; ongoing) Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Arm A (nivo+chemo/nivo)		Nivolumab 360 mg IV Q3W in combination with platinum-based doublet chemo (Q3W × 4 cycles) prior to surgery, followed by nivolumab 480 mg IV monotherapy (Q4W for 13 cycles) post-surgery.
	Arm B (placebo+chemo/placebo)		Placebo in combination with platinum-based doublet chemo (Q3W × 4 cycles) prior to surgery, followed by placebo (Q4W for 13 cycles) post-surgery.
Endpoints and definitions	Primary endpoint	EFS by BICR	EFS (by BICR per RECIST 1.1): time from randomization to any event of progression of disease or worsening of disease precluding surgery if surgery was attempted but gross resection was abandoned due to unresectable tumour or worsening of disease, progression or recurrence of disease after surgery, progression or recurrence of disease without surgery, or death due to any cause.
	Secondary endpoint	pCR by BIPR	pCR rate: the number of randomized subjects with absence of residual viable tumour in lung and lymph nodes as evaluated by BIPR, divided by the number of randomized subjects for each arm.
	Secondary endpoint	MPR by BIPR	MPR rate: the number of randomized subjects with ≤ 10% residual viable tumour in lung and lymph nodes as evaluated by BIPR, divided by the number of randomized subjects for each arm.
	Secondary endpoint	OS	OS: time between the date of randomization and the date of death due to any cause.
Database lock	26-Jul-2023 (interim EFS analysis). For the OS data, the DCO was 11-Nov-2024 (OS IA)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The EFS IA was conducted in 461 patients concurrently randomized to nivo+chemo/nivolumab (229) and placebo+chemo/placebo (232). Results reported below correspond to subjects with PD-L1 tumour cell expression ≥ 1%.		
Descriptive statistics and estimate variability	Treatment group	Nivo+chemo/nivolumab	Placebo+chemo/placebo
	Number of subjects	128	128
	EFS (median, months)	NR	15.80
	95% CI	(28.94, NR)	(9.33, 35.06)
	pCR (response rate [%])	35.2	4.7
	95% CI	(26.9, 44.1)	(1.7, 9.9)
	MPR (response rate [%]) 95% CI	45.3 (36.5, 54.3)	13.3 (7.9, 20.4)

Effect estimates per comparison	Primary endpoint: EFS	Comparison groups	Nivo+chemo/nivolumab vs. placebo+chemo/placebo
		HR	0.52
		95% CI	0.35, 0.78
	Secondary endpoint: pCR	Comparison groups	Nivo+chemo/nivolumab vs. placebo+chemo/placebo
		Difference in proportions	30.5
		95% CI	21.2. 39.4
	Secondary endpoint: MPR	Comparison groups	Nivo+chemo/nivolumab vs. placebo+chemo/placebo
		Difference in proportions	32.0
		95% CI	21.2, 41.9
	Secondary endpoint: OS* *DCO: 11-Nov-24	Comparison groups	Nivo+chemo/nivolumab vs. placebo+chemo/placebo
		HR	0.61
		95% CI	0.39, 0.97
Notes	CI= confidence interval; HR= hazard ratio; NR= not reached		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Table 35. Clinical studies in special populations

	Controlled Trials	Non-controlled trials
Paediatric patients <18 years (Subjects number /total number)	0	NA
Older patients; Age 65-74 (Subjects number /total number)	115/229 (50.2)	NA
Age 75-84 (Subjects number /total number)	12/229 (5.2)	NA
Age 85+ (Subjects number /total number)	0	NA

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C

In vitro biomarker test for patient selection for efficacy

Per the CA20977T protocol, an archival (or fresh) FFPE tissue block or 5-10 unstained tumour tissue sections (with an associated pathology report), was required to be collected within 3 months prior to enrolment. Tissue was required to be from a core needle biopsy, excisional or incisional biopsy. If an archived specimen was not available, a fresh tumour biopsy was to be collected.

Additional tumour samples were collected during surgical resection, which occurred after 4 cycles of

treatment in each arm. A third (optional) biopsy could have been collected at the time of disease progression.

Tumour PD-L1

Tumour tissue specimens were sent to the central lab for PD-L1 testing. PD-L1 in FFPE NSCLC human tissue was performed using IHC performed on Dako Autostainer Link 48 (labelled as IUO).

Validation of the PD-L1 IHC (clone 28-8) assay was performed in accordance with the provider Standard Operating Procedures (SOPs) and regulatory requirements to provide documentation of assay performance characteristics and to ensure validity of the data produced. The validation was approved for use 04-Dec-2013.Evaluation and interpretation of PD-L1 expression in tumour and normal tissues, along with stained control samples, was performed by a trained Pathologist using the criteria indicated in Dako's interpretation manual, PD-L1 IHC Pathologist Scoring Manual for BMS NSCLC Clinical Protocol.

PD-L1 expression was defined as the percent of tumour cells with membrane staining in a minimum of 100 evaluable tumour cells per validated Agilent/Dako PD-L1 IHC 28-8 pharmDx test. PD-L1 status was classified by a pathologist at a central lab as:

- PD-L1 expressing tumours: ≥ 1% tumour cells with membrane staining in a minimum of 100 evaluable tumour cells
- PD-L1 non-expressing tumours: < 1% tumour cells with membrane staining in a minimum of 100 evaluable tumour cells
- PD-L1 not quantifiable (includes indeterminate and not evaluable)

Supportive study(ies)

Not applicable.

2.4.3. Discussion on clinical efficacy

The finally agreed indication in this submission is as follows:

"OPDIVO, in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD L1 expression ≥ 1% (see section 5.1 for selection criteria)."

Design and conduct of clinical studies

The basis for this application is the study CA20977T, a Phase III, randomised, double-blind, placebo-controlled study.

The proposed regimen is nivolumab 360 mg Q3W in combination with platinum-based doublet chemo (4 cycles) prior to surgery, followed by adjuvant treatment with nivolumab 480 mg Q4W (13 cycles). The proposed regimens for both the neoadjuvant and adjuvant treatment are the same as the ones already approved for Opdivo in other indications, except for the number of cycles recommended for nivolumab: 3 as neoadjuvant treatment for NSCLC instead of the 4 cycles proposed in this submission.

The MAH did not seek scientific advice from the CHMP for this study.

Design of the study

The study included patients with resectable Stage IIA-IIIB NSCLC (AJCC 8th edition), either squamous or non-squamous, who have not received prior treatment for resectable NSCLC. The study enrolled patients regardless of their PD-L1 expression level. Subjects with N3 nodal disease, brain metastasis, EGFR mutations (regardless of mutation type), or known ALK mutations were excluded. Patients with non-squamous tumours with unknown EGFR mutation status had to be tested for EGFR mutation. Postoperative radiotherapy (PORT) was permitted for patients in whom it was indicated, according to local guidance.

Patients were randomized in a 1:1 ratio to receive nivolumab 360 mg Q3W for 4 cycles in combination with platinum-based doublet chemo prior to surgery, followed by nivolumab 480 mg as monotherapy Q4W for 13 cycles after surgery; or placebo Q3W for 4 cycles in combination with platinum-based doublet chemo prior to surgery, followed by placebo Q4W for 13 cycles after surgery. Stratification factors were tumour histology (squamous vs. non-squamous), NSCLC stage (II vs. III), and PD-L1 status (≥1% vs. <1% vs. indeterminate/not evaluable). Stratification factors are in line with other studies in this setting and with the Guideline on the evaluation of anticancer medicinal products in man – condition specific guidance (EMA/CHMP/703715/2012 Rev. 2).

Chemotherapy schemes allowed in the neoadjuvant phase depended on the tumour histology and Investigator's discretion: for squamous tumours the options were carboplatin + paclitaxel and cisplatin + docetaxel; whereas for non-squamous tumours the options were carboplatin + paclitaxel, carboplatin + pemetrexed and cisplatin + pemetrexed. Initially for squamous tumours carboplatin + docetaxel was also allowed, but in the second amendment of the protocol this regimen was removed.

The primary endpoint of this study was EFS by BICR, which is considered an adequate endpoint to measure clinical benefit in this (neo)-adjuvant setting. Key secondary endpoints were OS, pCR by BIPR and MPR by BIPR. Exploratory endpoints were ORR by BICR; TTDM by investigator; EFS, MPR and pCR by PD-L1 status; and EFS2 per investigator. Other exploratory endpoints were: EQ-5D-3L VAS & UI scores, PROMIS T scores, FACT-L and NSCLC-SAQ scores, GP5 scores from the FACT-L and NSCLC-SAQ scores. Overall, secondary and exploratory endpoints are also considered adequate. pCR and MPR are not yet validated surrogate endpoints in NSCLC and therefore they cannot serve for regulatory decision making at this point, but they are considered supportive since they provide information about treatment's antitumour activity. OS in the context of this potentially curative (neo)-adjuvant setting is considered critical to allow a proper B/R assessment.

One of the main limitations of the design of this study is the impossibility to isolate the effect of the neoadjuvant therapy from the effect of the adjuvant therapy. This design impairs elucidating whether the potential benefits in the nivolumab arm are due to the neoadjuvant phase or to the adjuvant phase; and therefore whether the two phases are needed to obtain the observed benefit, or, on the contrary, whether the administration of nivolumab in any of the two phases (i.e., as neoadjuvant treatment or as adjuvant treatment) would have resulted in similar clinical outcomes without exposing patients to unnecessary toxicity.

Statistical methods

The sample size of this study is calculated to compare EFS between Arm A and Arm B under a two-side 0.05 type I error with 90% power consideration. The number of events was estimated assuming an exponential distribution for EFS in each arm. The methodology for calculating the sample size is considered acceptable and raises no concerns.

An EFS interim analysis was scheduled to take place after 185 events (80% of the total number of events), which corresponds to approximately 32 months after the first subject is randomized. If

superiority of EFS per BICR assessment for the comparison between treatment groups was demonstrated at a two-sided type I error rate 0.05, OS would be tested hierarchically. One interim analysis was planned at the time of the EFS FA (where 80% of the total number of events were projected to have occurred around 140 events).

The hierarchical testing strategy is considered acceptable and is not expected to inflate the type I error. The administrative alpha penalty applied by the MAH to prevent from potential inflation of the type I error due to the submission of OS descriptive summaries is also considered acceptable.

The techniques used to estimate EFS and to handle the interim analyses are acceptable. Two definitions on strategy with subsequent anti-cancer therapy prior to events have been considered: following the "while on treatment strategy" in the first definition and the "treatment policy approach" as second definition for this intercurrent event. On the other hand, for the secondary objective, overall survival was considered regardless of whether the patient withdrew from study treatment or received another anti-cancer therapy prior to progression, following the "treatment policy approach" for these intercurrent events. Therefore, regarding handling of intercurrent events, the MAH provided a clear and detailed definition and discussion on all endpoints. These approaches are acceptable.

The MAH planned several sensitivity analyses for EFS to address potential biases. Different scenarios concerning censoring rules, model assumptions, impact of Russia exit or potential delayed treatment effect of experimental treatment were considered to address these biases. These supportive analyses are useful.

With regards to supportive analyses for OS, a multivariate Cox regression model, an un-stratified Cox model, OS analysis for participants with no relevant protocol deviations or using population excluding patients from Russia were planned, which is acceptable.

Conduct of the study

During the conduct of the study, the MAH implemented 3 **amendments to the protocol**. In the first amendment (dated 20-Dec-2019), the MAH added EFS and OS comparisons by tumour PD-L1 status as an exploratory objective and added additional chemo regimens, together with other modifications. In the second amendment (dated 11-May-2020) the MAH updated tumour PD-L1 stratification from ≥1% or <1% which includes indeterminate or not evaluable to PD-L1 ≥1% or < 1% or indeterminate or not evaluable per health authority request, clarified the inclusion criteria for tumour eligibility, and removed carboplatin + docetaxel as a chemo regimen for subjects with SQ histology, among other changes. In the third amendment (dated 20-Apr-2021) the MAH implemented some changes related to the COVID-19 pandemic. Overall, it does not seem that the amendments implemented could have impacted the observed results.

The percentage of relevant protocol deviations is low (1.7% in the nivolumab arm vs. 3% in the placebo arm), suggesting that the protocol deviations did not impact on the observed results.

Efficacy data and additional analyses

The data submitted are based on the results of the interim analysis of EFS (DCO: 26-Jul-23; IF: 81.8%), which met statistical significance; and on the results of the interim analysis of OS (DCO: 11-Nov-2024; IF: 80%). The EFS and OS analyses presented in this submission were the only interim analyses planned. At the time of submission of the results of the OS IA the MAH also presented an EFS update.

At EFS IA (DCO: 26-Jul-23), 735 patients were enrolled into the study and 461 were randomized (229 to nivo+chemo/nivolumab vs. 232 to placebo+chemo/placebo). It is noted that the number of patients

included in this study is smaller than in other studies in the same setting. Almost all patients received neoadjuvant treatment (99.6% in the nivolumab arm vs. 99.1% in the placebo arm). Of these, 85.1% of patients in the nivolumab arm vs. 89.1% in the placebo arm completed neoadjuvant treatment. Of note, these percentages refer to the total neoadjuvant treatment, which includes both nivolumab/placebo and chemotherapy. In this context it is important to know whether the administration of nivolumab adversely affects the completion of treatment with chemotherapy. Reassuringly, the percentage of patients who completed treatment with chemotherapy was high and similar among both arms (77.8% - 89.4% in the nivolumab arm, vs. 79% - 86% in the placebo arm), with only 2 subjects (1 in each arm) discontinuing chemotherapy while receiving 4 cycles of nivo/placebo. In both cases they had to discontinue chemotherapy because of AEs commonly associated with chemotherapy; therefore it does not seem that the administration of nivolumab negatively impacted on the administration of the planned number of chemotherapy cycles. The most common reason for discontinuation of neoadjuvant treatment was study drug toxicity in both arms: 9.2% in the nivolumab arm vs. 4.8% in the placebo arm.

Importantly, a similar percentage of patients had definitive surgery in both arms: 77.7% in the nivolumab arm vs. 76.7% in the placebo arm. Since, in this setting, surgical resection is considered to be of curative intent, the fact that the administration of nivolumab in the neoadjuvant phase did not translate into a lower percentage of patients completing surgery is reassuring; at least in terms of the effects of nivolumab in the neoadjuvant phase of treatment. However, around 20% of patients did not undergo surgery (46 [20.1%] in the nivolumab arm vs. 50 [21.6%] in the placebo arm). The main reasons for cancelled surgery were "subject refusal" (23.9% in the nivolumab arm vs. 16% in the placebo arm), "surgeon decision" (17.4% vs. 12%), "radiographic progression precluding surgery" (17.4% vs. 36%) and "adverse events" (15.2% vs. 8%). The percentage of patients with surgery abandoned was low in both arms: 1.3% in the nivolumab arm vs. 1.7% in the placebo arm; and the reasons for abandoning the surgery were mainly because of "unresectable tumour or worsening of disease".

No relevant differences between arms were observed in terms of the surgical procedures, apart from a higher percentage of patients with a single lobectomy in the nivolumab arm, compared with the placebo arm (79.8% in the nivolumab arm vs. 71.9% in the placebo arm). Similarly, no differences were observed in terms of subjects with delayed surgery (20.2% in the nivolumab arm vs. 18.5% in the placebo arm). The percentage of R0 resections for patients who completed the surgery was high and similar in both treatment arms (89.3% in the nivolumab arm vs. 90.4% in the placebo arm), suggesting that there is no clear correlation between neoadjuvant treatment with nivolumab and a higher percentage of patients with R0 resections.

After surgery, there were 39 patients in the nivolumab arm and 29 patients in the placebo arm who did not receive adjuvant therapy treatment. In the nivolumab arm the most common reason for not continuing with the adjuvant treatment was "study drug toxicity" (13 patients; 33.3%), followed by "AE unrelated to study drug" (7 patients; 17.9%). It is also noted that in this period there were 2 deaths in the nivolumab arm, while no deaths were reported in the placebo arm. In the placebo arm the most common reason for not continuing with the adjuvant treatment was "disease progression/recurrence", accounting for 48.3% of patients (14 patients).

At EFS IA DCO, there were only 16 patients ongoing on adjuvant treatment (8 in each arm). Around 60% of patients who started adjuvant treatment (59.9% in the nivolumab arm vs. 60.5% in the placebo arm) completed adjuvant treatment in each arm; meaning that only around 40% (37% of patients in the nivolumab arm and 40% in the placebo arm) of patients who were randomized completed the neoadjuvant + adjuvant treatment. The most common reason for discontinuation of adjuvant treatment in the nivolumab arm was "study drug toxicity" (12% vs. 2% in the placebo arm),

while in the placebo arm it was "disease progression/recurrence" (24.3% vs. 11.3% in the nivolumab arm). These low completion percentages put into question the feasibility of the proposed regimen. At OS IA DCO, all subjects had completed or discontinued treatment except for 4 Russian subjects and whose end of treatment status could not be updated.

Baseline characteristics

Overall, baseline characteristics were well-balanced between both arms.

Regarding demographic characteristics, there were more males included in the study than females (70.9% males vs. 29.1 females), reflecting the expected target population. Additionally, there was a lower percentage of White patients included in the nivolumab arm than in the placebo arm (67.7% in the nivolumab arm vs. 75.4% in the placebo arm), which was in turn compensated by a higher percentage of Asian patients in the nivolumab arm (28.8% in the nivolumab arm vs. 21.6% in the placebo arm). Regarding smoking history, most patients in both arms were current or former smokers (90.5%) compared with the never smokers (9.5%).

Regarding disease characteristics, the majority of patients had stage III disease. The most frequent sub-stage was IIIA, with 47.1% of patients; followed by IIB (28%) and IIIB (16.9%). 7.2% of patients had stage IIA, 0.4% (2 patients; both of them in the nivolumab arm) had stage IIIC; and 0.4% (2 patients; both of them in the placebo arm) had stage IV. The percentage of patients with squamous and non-squamous tumours was similar, accounting for around 50% each. Most patients in both arms had a baseline ECOG PS status of 0 (62.5%). Regarding PD-L1 status, most patients had TC ≥1% (55.5%), of these 21% had TC ≥50%. There were 3.5% of patients in the nivolumab arm and 4.7% in the placebo arm with not evaluable PD-L1 status.

The number of patients who received PORT was the same in both arms: 12 patients (5.3% in the nivolumab arm vs. 5.2% in the placebo arm). Considering the low number of patients who received PORT, and that the percentages between arms were well-balanced, it is not considered that the administration of PORT could have impacted to a great extend the results.

Results

EFS, the primary endpoint, met the boundary for statistically significance at the IA, with a HR of 0.58 (97.36% CI 0.42, 0.81); p-value: 0.00025. At the IA there were 189 EFS events: 76 events (33.2%) in the nivolumab arm vs. 113 events (48.7%) in the placebo arm. Most of the events in both arms were due to "progression/recurrence after surgery" (15.7% in the nivolumab arm vs. 33.2% in the placebo arm), followed by "death" (7.4% in the nivolumab arm vs. 3.4% in the placebo arm) and by "progression/worsening disease precluding surgery" (6.1% in the nivolumab arm vs. 9.5% in the placebo arm). mEFS was 18.43 (95% CI: 13.63, 28.06) months in the placebo arm, while it was not reached (95% CI: 28.94, NA) in the nivolumab arm. The KM curve shows clear separation at around month 3. Of note, this IA was conducted at an information fraction of 81.8%, with a minimum FU of 15.7 months and a median FU of 25.4 months. The percentage of censored patients was 66.8% in the nivolumab arm and 51.3% in the placebo arm; being the majority of patients in the follow-up phase of the study (51.1% in the nivolumab arm vs. 34.9% in the placebo arm). Of note, only 8 patients (3.5%) in the nivolumab arm and 7 patients (3%) in the placebo arm remained on adjuvant treatment at the date of the DCO of the EFS IA. The MAH provided an updated descriptive analysis of EFS (DCO: 11-Nov-2024) with a median follow-up of 41.0 months; which accounts for around 15 additional months of follow-up. At the DCO for this updated analysis, there were 212 events reported (88 in nivolumab and 124 in placebo). The results provided, with a longer follow-up, were very similar to the results of the primary analysis. The HR for the updated analysis is 0.61 (95% CI: 0.46, 0.80), and the KM curves remained similar. mEFS was 46.55 months (95% CI: 35.81, NA) in the nivolumab arm vs. 16.92 months (95% CI: 13.57, 28.19) in the placebo arm. The final EFS analysis – which will be

descriptive – is planned when 231 events would occur. Since no major difference is expected between this DCO and the FA (only 20 additional events should occur), the results of this final analysis are not considered critical for the B/R assessment, and can be submitted together with the FA OS results whenever the FA OS results are available (see **ANX-II**). Several sensitivity analyses were conducted, showing robustness in the treatment effects.

Moreover, with the aim of analysing the discrepancy between PFS assessed by the Investigator (HR: 0.56; 95% CI: 0.41, 0.76) and the BICR, the MAH has conducted a concordance comparison, drawing a 92.6% agreement on progressions and non-progressions in the nivolumab arm, and a 95.3% agreement in the placebo arm.

pCR and **MPR,** secondary endpoints, resulted in relevant differences in favour of nivolumab over placebo. pCR in nivolumab was 25.3% (95% CI: 19.8, 31.5) vs. 4.7% (95% CI: 2.4, 8.3) in placebo; and MPR was 35.4% (95% CI: 29.2, 41.9) vs. 12.1% (95% CI: 8.2, 17.0). It is noted that for both endpoints CIs between the nivolumab arm and the placebo arm are far from overlapping. The differences between arms were 20.5 (95% CI: 14.3, 26.6) for pCR; and 23.2 (95% CI: 15.8, 30.6) for MPR.

With regards to **EFS2** (exploratory endpoint), results also favoured nivolumab over placebo [HR: 0.83 (95% CI: 0.56, 1.23)], although statistical significance was not reached, with a separation of the KM curves at around month 21.

Regarding **PROs**, the MAH has provided results of NSCLC-SAQ, FACT-L, EQ-5D-3L (EQ-5D-3L VAS and UI scores), PGI-S and PROMIS physical function. Overall, patients had similar results with nivolumab than with placebo, with no remarkable differences between arms. Some PROs resulted in slight improvements (i.e., FACT-L and EQ-5D-3L VAS) in the overall period – which includes the neoadjuvant, surgical and adjuvant periods – whereas other PROs resulted in slight worsening (i.e., NSCLC-SAQ, EQ-5D-3L UI and PROMIS physical function). Although none of these slight improvements or worsening reached the pre-specified minimally important difference, median time to deterioration was overall longer with nivolumab than with placebo, in all the PROs.

At EFS IA, **OS** data were immature (88 OS events; 50% IF approx.; mFU: 25.4 months) and no formal statistical analysis was conducted. Upon request, the MAH provided the results of the OS IA, which was triggered by the number of OS events [140 events (80% IF); DCO: 11-Nov-2024]. At OS IA, the HR point estimate was 0.85 (97.63% CI: 0.58, 1.25; 95% CI: 0.61, 1.18), with median OS not reached in any arm. Of note, although no apparent detriment in OS is observed, at the interim analysis OS did not reach statistical significance either. In the nivolumab arm there were 55 events (24 %) vs. 64 events (27.6 %) in the placebo arm. The main reason for censoring in both arms was that patients were in follow-up (66.8 % in the nivolumab arm vs. 59.9 % in placebo arm). It is also noted that KM curves overlap until approximately month 21, when a separation seems to be observed. OS rate at 30 months was 78.0 (95% CI: 71.8, 83.0) in the nivolumab arm, vs. 72.3 (95% CI: 65.8, 77.8) in the placebo arm. Importantly (and as expected), there was a higher rate of patients receiving any subsequent therapy in the placebo arm than in the nivolumab arm: 43.5% of patients in the placebo arm vs. 29.3% in the nivolumab arm. 29.3% of patients in the placebo arm (vs. 8.3% in the nivolumab arm) received an anti-PD-1/anti-PD-L1. This might certainly also play a role in the observed results. All things considered, and since the OS results seem to discard a detrimental OS effect, the OS data so far available are deemed enough as to reach a conclusion on the positive B/R of nivolumab in the finally proposed indication. Nevertheless, the MAH has committed to submit the results of the final OS analysis (including subgroup analyses) as an Annex-II condition (**ANX**) in order to verify the impact of the intervention on overall survival and confirm previous efficacy assumption, in the context of an approval based on EFS.

Subgroup analyses

Overall, no relevant differences in **EFS** by subgroups were observed. Patients who have never smoked had worse outcomes than patients who were current or former smokers; but due to the small size of the subgroup (only 44 patients had never smoked), no conclusions can be drawn. Moreover, it seems that EFS outcomes are slightly worse for patients with Stage II (HR: 0.81; 95% CI: 0.46, 1.43) than for patients with Stage III, per CRF (. HR: 0.51; 95% CI: 0.36, 0.72); less favourable for patients with non-squamous tumours [HR: 0.72 (95% CI: 0.49, 1.07)] than for patients with squamous tumours [HR: 0.46 (95% CI: 0.30, 0.72)].

The MAH presented additional EFS (per BICR) by surgery (with or without); by pCR and MPR status; and by adjuvant treatment received or not received. Although it is difficult to interpret the results of such analyses, it seems that patients who had surgery had better outcomes than patients who did not have surgery; patients who had pCR or MPR had better outcomes than patients who did not had pCR or MPR, and that patients who received adjuvant treatment had better outcomes than patients who did not receive it. Additionally, it seems that the patients who only received nivolumab as neoadjuvant (and did not receive adjuvant therapy) also benefitted from the treatment, since EFS outcomes were better for them than for patients who received placebo. Nevertheless, no firm conclusions can be drawn from the available data so far. Updated EFS subgroup analyses (DCO: 11-Nov-2024) were overall consistent with the primary analysis.

The MAH provided the results from **OS** subgroup analyses, based on the interim OS analysis (DCO: 11-Nov-2024). In the provided analyses it is observed that the results of some subgroups are relevantly different from the results in the overall population, suggesting the existence of some heterogeneity between subgroups which is concerning. Notably, it should be highlighted that the OS results in the subgroup of PD-L1 < 1% patients (N=186) were markedly worse than the results in the PD-L1 ≥ 1% subgroup (N=256): the HR for the subgroup of PD-L1 < 1% patients was 1.19 (95% CI: 0.72, 1.97), while the HR for the subgroup of PD-L1 ≥ 1% patients was 0.61 (95% CI: 0.39, 0.97). The KM curves of the subgroup of PD-L1 < 1% patients suggest a detrimental OS effect in this subgroup of patients; with the nivolumab curve laying above the placebo curve for almost the whole follow-up period. Looking at other endpoints, the effect in EFS (DCO: 11-Nov-2024) was also lower in the subgroup of patients with PD-L1 < 1% (HR 0.79; 95% CI: 0.52, 1.21) compared with those with PD-L1 ≥ 1% (HR 0.53; 95% CI: 0.36, 0.76). Besides, lower pCR (12.9% nivolumab vs. 4.3% placebo), MPR (21.5% vs. 9.7%) and ORR (53.8% vs. 43.0%) were also observed in the subgroup of patients with PD-L1 < 1% compared with the subgroup of patients with PD-L1≥1% (pCR: 35.2% vs. 4.7%; MPR: 45.3% vs. 13.3%; ORR: 60.9% vs. 43.8%) at the initial DCO (26-Jul-2023).

While it is acknowledged that OS was a secondary endpoint of the study, the observed possible detrimental effect in OS in the subgroup of patients with a lower PD-L1 expression (40% of the patient population) is of concern, particularly considering the added toxicity of nivolumab and the need for a longer treatment exposure by including the adjuvant phase. Additionally, it is noted that the efficacy assessment by PD-L1 expression was an exploratory objective of the study, and that PD-L1 status was a stratification factor. Considering the biological plausibility of a differential effect by PD-L1 expression, and the similar finding for other PD1 / PD-L1 inhibitors in NSCLC indications (particularly the results from study Checkmate 816 studying nivolumab as neoadjuvant in the same setting), such subgroup finding was considered credible as per the Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013). In light of these results, the MAH agreed to restrict the indication to patients with a PD-L1 expression ≥ 1%.

The results in some other subgroups are also noteworthy to mention. By histology, in the non-squamous subgroup (N=227) the results seemed inferior to the squamous subgroup (N=234): in the non-squamous subgroup the HR was 0.94 (95% CI: 0.59, 1.52), while in the squamous subgroup the

HR was 0.73 (95% CI: 0.46, 1.16). One plausible justification for the observed difference could be the higher percentage of subjects with PD-L1 < 1% - associated with worse outcomes - in the non-squamous subgroup (50.4% in nivolumab and 48.2% in placebo) compared with the squamous subgroup (31% in nivolumab and 32.2% in placebo). In order to further investigate this finding, the MAH submitted OS data by histology (squamous/non-squamous) and by PD-L1. These data showed that there was a clear difference between PD-L1 ≥1% and PD-L1 <1% patients (regardless of the histology), with unfavourable HR point estimates for the PD-L1 <1% patients and favourable HR point estimates for the PD-L1 ≥1% patients. Since the indication was finally restricted to PD-L1 ≥1% patients, this concern is considered to be alleviated.

Additionally, in the Stage II subgroup (N=161) the HR was 0.93 (95% CI: 0.49, 1.78), whereas in the Stage III subgroup (N=298) the HR was 0.82 (95% CI: 0.56, 1.22). In this case the percentage of PD-L1 <1% patients were similar in both subgroups, thus, the finding cannot be explained by a higher percentage of patients with PD-L1 expression <1% in the Stage II subgroup. It is noted that the low number of events in Stage II patients, and, particularly, in Stage II PD-L1 <1% patients (nivo: 5 OS events; placebo: 7 OS events) impairs drawing any firm conclusion in this regard. All things considered, the most plausible reason for the observed results in Stage II patients is the lower number of Stage II patients and events compared to the number of Stage III patients and events; which, inevitably, leads to higher uncertainties in terms of the estimations. Provision of final OS analysis as annex II condition could provide a more precise estimation of the OS effect in the patients enrolled with stage II disease.

Wording of the indication

The initially proposed indication in this submission was: "*OPDIVO, in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment after surgical resection, is indicated for the treatment of adult patients with resectable non-small cell lung cancer (see section 5.1)*".

At the initial stages of the procedure the MAH was requested to modify the indication to reflect that patients included should be at high risk of recurrence. Additionally, during the procedure some uncertainties regarding the benefit in PD-L1 < 1% were identified, leading to the restriction of the indication to patients with PD-L1 expression ≥1%. Therefore, the finally proposed indication is as follows (***text added***; ~~*text deleted*~~):

"OPDIVO, in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment ~~*after surgical resection*~~*, is indicated for the treatment of resectable non-small cell lung cancer* ***at high risk of recurrence in adult patients whose tumours have PD L1 expression ≥ 1% (see section 5.1 for selection criteria).***"

The wording of the indication is considered acceptable.

A wording was included in section 5.1 of the SmPC to reflect the tumour types who were eligible for enrolment in the study according to the 8th edition AJCC/UICC staging criteria : Stage IIA (> 4 cm) to IIIB (T3-T4 N2). Further description of the corresponding tumour characteristics were provided : any patient with a tumour size > 4 cm; any patient with N1 or N2 disease (regardless of primary tumour size); patients with multiple tumour nodules in either the same lobe or different ipsilateral lobes; patients with tumours that are invasive of thoracic structures (directly invade visceral pleura, parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus; or tumours that are associated with atelectasis or obstructive pneumonitis that extends to the hilar region or involves the entire lung.

2.4.4. Conclusions on the clinical efficacy

The results of the CA20977T study (IA) showed a statistically significant improvement in its primary endpoint, EFS by BICR. Additionally, although OS did not reach statistical significance in its interim analysis, no detrimental effect is observed either, which is reassuring considering that long-term outcomes in terms of OS are considered critical in this potentially curative setting. The EFS and OS data so far available are considered robust enough as to conclude on the positive B/R of nivolumab in this setting, although in order to further characterise the long-term OS benefit, the MAH has committed to submit the results of the final OS analysis (including subgroup analyses) as an Annex-II condition (**ANX**).

Importantly, the results of the OS subgroup analyses revealed a potential detrimental effect in patients with PD-L1 expression <1% (40% of the patient population). Considering the added toxicity of nivolumab and the need for a longer treatment exposure by including the adjuvant phase, the indication was restricted to patients with a PD-L1 expression ≥1%.

The following measures are considered necessary to address issues related to efficacy:

Post authorisation efficacy study (PAES): In order to further characterise the long-term efficacy of OPDIVO in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment, for the treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD L1 expression ≥ 1%, the MAH should submit the results of the final OS analysis from study CA20977T, a phase III, randomised, double-blind study. The results should be provided by 30 June 2027

2.5. Clinical safety

Introduction

Drug exposure and safety analyses in CA20977T are performed for the All Treated Subjects (n = 458), which includes all subjects from the *Global Population* (i.e., all subjects randomized within the global accrual window; N = 461) who received at least one dose of any study medication in the neoadjuvant or adjuvant setting.

As of the clinical cut-off date of 26-Jul-2023, a total of 461 subjects were included in the global population (229 randomized to nivo+chemo/nivolumab and 232 randomized to placebo+chemo/placebo) and 458 subjects were treated (228 and 230, respectively). At the time of the data cut-off, the median follow-up was 25.4 months (minimum: 15.7 months) among all randomized subjects in this population (Table 36). Unless otherwise specified, the safety data presented in this section are based on the cut-off date of 26-Jul-2023.

Table 36. Key Dates and Follow-up - All Enrolled Subjects in the Global Population in CA20977T

FPFV	05-Nov-2019
Clinical Cutoff Date	26-Jul-2023
Minimum follow-up[a], months	15.7 months
Median follow-up[b], months	25.4 months

[a] Minimum follow-up: time from last subject's randomization to clinical cutoff date for DBL.

[b] Median follow-up: median time between randomization date and last known alive date (for subjects who are alive) or death.

In the nivo+chemo/nivolumab and placebo+chemo/placebo arms, respectively, 178/229 (77.7%) and 178/232 (76.7%) randomized subjects underwent definitive surgery, and 142/228 (62.3%) and 152/230 (66.1%) treated subjects received adjuvant therapy.

Descriptive statistics of safety were presented using NCI CTCAE version 4.0 by treatment group. All on-study AEs, drug-related AEs, SAEs, drug-related SAEs, IMAEs, select AEs, and OESIs were tabulated using worst grade by system organ class (SOC) and preferred term (PT). On-study laboratory parameters including haematology, chemistry, liver function and renal function were summarized using worst grade. Frequency, management, and resolution of IMAEs and select AEs were analysed. The incidence of AEs/SAEs indicated as surgical complications in the CRF, up to 90 days after surgery was summarized by worst CTC grade, by treatment group. AEs leading to cancellation of surgery and leading to surgery delay were summarized by worst CTC grade, by treatment group.

The periods of the study are defined as follows:

- Neoadjuvant: includes the period from the first dose of neoadjuvant therapy through 30 days (or 100 days for "extended follow-up" analyses) either after the last dose of neoadjuvant therapy, before the date of surgery, or through the initiation of adjuvant therapy, whichever was earlier.
- Surgery: includes the period from the date of definitive surgery through 90 days after definitive surgery or through the initiation of adjuvant therapy, whichever was earlier.
- Adjuvant: includes the period from the first dose of adjuvant therapy through 30 days (or 100 days for "extended follow-up" analyses) after the last dose of adjuvant therapy.
- Overall: includes the neoadjuvant treatment period (as defined above), the pre- and post-surgery treatment periods, and the adjuvant treatment period (as defined above).

Note that AEs with an onset date during the neoadjuvant period that continued into the adjuvant period were only counted in the neoadjuvant period, except if there was a change in the grade. If there was a change in the grade in the adjuvant period, the AE was counted in both the neoadjuvant and adjuvant periods. However, the duration of AEs, time to onset, and time to resolution were calculated using the entire treatment period.

Patient exposure

The median duration of therapy in the overall treatment period including neoadjuvant study drug (nivo+chemo or placebo+chemo), definitive surgery, PORT (when indicated) and adjuvant study drug (nivolumab or placebo) was numerically shorter in the nivo/chemo+nivolumab arm compared to the placebo/chemo+placebo arm (10.30 months vs. 12.57 months, respectively).

The median duration of adjuvant therapy was the same in both arms.

Table 37. Duration of Study Therapy Summary – All Treated Subjects in Global Population

	Arm A: Nivo + Chemo/Nivo N = 228	Arm B: Placebo + Chemo/Placebo N = 230
DURATION OF OVERALL THERAPY (MONTHS)		
MEAN (MIN, MAX)	9.85 (0.0, 22.3)	10.49 (0.0, 26.9)
MEDIAN	10.30	12.57
> 3 MONTHS (%)	172 (75.4)	177 (77.0)

> 6 MONTHS (%)	141 (61.8)	149 (64.8)
> 9 MONTHS (%)	120 (52.6)	135 (58.7)
> 12 MONTHS (%)	101 (44.3)	120 (52.2)
DURATION OF ADJUVANT THERAPY (MONTHS)		
N	142	152
MEAN (MIN, MAX)	8.69 (0.0, 15.2)	9.22 (0.0, 21.2)
MEDIAN	11.07	11.07
> 3 MONTHS (%)	120 (84.5)	138 (90.8)
> 6 MONTHS (%)	103 (72.5)	124 (81.6)
> 9 MONTHS (%)	91 (64.1)	107 (70.4)
> 12 MONTHS (%)	8 (5.6)	8 (5.3)

Similar proportions of subjects in the nivo+chemo/nivolumab and placebo+chemo/placebo arms completed the neoadjuvant treatment period (85.1% vs 89.1%), had definitive surgery (77.7% vs 76.7%), and completed the adjuvant treatment period (59.9% vs 60.5%). A total of 39 subjects in the nivo+chemo/nivolumab arm and 29 subjects in the placebo+chemo/placebo arm underwent surgery but did not have adjuvant treatment. Overall, 60.2% completed the adjuvant treatment period, 34.4% discontinued adjuvant treatment, and 5.4% of subjects were ongoing in the adjuvant treatment period.

See Table 10. Subject Disposition by Period - Subjects in the Global Population

Neoadjuvant Treatment Period

Most subjects (83.8% for nivo; range for the chemo agents: 77.8% - 89.4%) received 4 cycles of neoadjuvant therapy (Table 38). In both arms, paclitaxel/carboplatin was the most frequently administered chemotherapy regimen.

Table 38. Cumulative Dose and Relative Dose Intensity of Neoadjuvant Therapy - All Treated Subjects in the Global Population

	Arm A: Nivo + Chemo/Nivo N = 228		
	Nivolumab N = 228	Cisplatin N = 60	Docetaxel N = 10
NUMBER OF DOSES RECEIVED			
NUMBER OF SUBJECTS RECEIVED 1 DOSE	14 (6.1)	3 (5.0)	1 (10.0)
NUMBER OF SUBJECTS RECEIVED 2 DOSES	14 (6.1)	5 (8.3)	1 (10.0)
NUMBER OF SUBJECTS RECEIVED 3 DOSES	9 (3.9)	1 (1.7)	0
NUMBER OF SUBJECTS RECEIVED 4 DOSES	191 (83.8)	51 (85.0)	8 (80.0)
MEAN (SD)	3.7 (0.85)	3.7 (0.84)	3.5 (1.08)
MEDIAN (MIN - MAX)	4.0 (1 - 4)	4.0 (1 - 4)	4.0 (1 - 4)
CUMULATIVE DOSE (1)			
MEAN (SD)	1314.5 (307.42)	266.8 (62.56)	245.4 (75.11)
MEDIAN (MIN - MAX)	1440.0 (360-1440)	297.0 (75-311)	273.2 (75-306)
RELATIVE DOSE INTENSITY (%)			
>= 110%	0	0	0
>= 90%	206 (90.4)	48 (80.0)	7 (70.0)
90% TO < 110%	206 (90.4)	48 (80.0)	7 (70.0)
70% TO < 90%	18 (7.9)	9 (15.0)	2 (20.0)
50% TO < 70%	4 (1.8)	3 (5.0)	1 (10.0)
< 50%	0	0	0
	Pemetrexed N = 104	Paclitaxel N = 117	Carboplatin N = 172
NUMBER OF DOSES RECEIVED			
NUMBER OF SUBJECTS RECEIVED 1 DOSE	5 (4.8)	8 (6.8)	11 (6.4)
NUMBER OF SUBJECTS RECEIVED 2 DOSES	4 (3.8)	9 (7.7)	11 (6.4)
NUMBER OF SUBJECTS RECEIVED 3 DOSES	2 (1.9)	9 (7.7)	11 (6.4)
NUMBER OF SUBJECTS RECEIVED 4 DOSES	93 (89.4)	91 (77.8)	139 (80.8)

MEAN (SD)	3.8 (0.74)	3.6 (0.90)	3.6 (0.87)
MEDIAN (MIN - MAX)	4.0 (1-4)	4.0 (1-4)	4.0 (1-4)
CUMULATIVE DOSE (1)			
MEAN (SD)	1836.8 (376.33)	636.4 (174.82)	18.9 (5.13)
MEDIAN (MIN - MAX)	1983.1 (485-2075)	698.8 (130-877)	20.0 (4-26)
RELATIVE DOSE INTENSITY (%)			
>= 110%	0	0	1 (0.6)
>= 90%	83 (79.8)	83 (70.9)	122 (70.9)
90% TO < 110%	83 (79.8)	83 (70.9)	121 (70.3)
70% TO < 90%	17 (16.3)	33 (28.2)	44 (25.6)
50% TO < 70%	3 (2.9)	1 (0.9)	5 (2.9)
< 50%	1 (1.0)	0	1 (0.6)

	Arm B: Placebo + Chemo/Placebo N = 230		
	Placebo N = 230	Cisplatin N = 48	Docetaxel N = 7
NUMBER OF DOSES RECEIVED			
NUMBER OF SUBJECTS RECEIVED 1 DOSE	9 (3.9)	5 (10.4)	1 (14.3)
NUMBER OF SUBJECTS RECEIVED 2 DOSES	7 (3.0)	1 (2.1)	0
NUMBER OF SUBJECTS RECEIVED 3 DOSES	9 (3.9)	4 (8.3)	0
NUMBER OF SUBJECTS RECEIVED 4 DOSES	205 (89.1)	38 (79.2)	6 (85.7)
MEAN (SD)	3.8 (0.68)	3.6 (0.97)	3.6 (1.13)
MEDIAN (MIN - MAX)	4.0 (1 - 4)	4.0 (1 - 4)	4.0 (1 - 4)
CUMULATIVE DOSE (1)			
MEAN (SD)	N.A.	257.4 (70.89)	243.5 (77.83)
MEDIAN (MIN - MAX)	N.A.	294.1 (75-312)	259.6 (75-301)
RELATIVE DOSE INTENSITY (%)			
>= 110%	N.A.	0	0
>= 90%	N.A.	40 (83.3)	4 (57.1)
90% TO < 110%	N.A.	40 (83.3)	4 (57.1)
70% TO < 90%	N.A.	7 (14.6)	3 (42.9)
50% TO < 70%	N.A.	1 (2.1)	0
< 50%	N.A.	0	0

	Pemetrexed N = 95	Paclitaxel N = 129	Carboplatin N = 186
NUMBER OF DOSES RECEIVED			
NUMBER OF SUBJECTS RECEIVED 1 DOSE	6 (6.3)	5 (3.9)	9 (4.8)
NUMBER OF SUBJECTS RECEIVED 2 DOSES	4 (4.2)	4 (3.1)	6 (3.2)
NUMBER OF SUBJECTS RECEIVED 3 DOSES	3 (3.2)	6 (4.7)	11 (5.9)
NUMBER OF SUBJECTS RECEIVED 4 DOSES	82 (86.3)	114 (88.4)	160 (86.0)
MEAN (SD)	3.7 (0.83)	3.8 (0.69)	3.7 (0.74)
MEDIAN (MIN - MAX)	4.0 (1 - 4)	4.0 (1 - 4)	4.0 (1 - 4)
CUMULATIVE DOSE (1)			
MEAN (SD)	1793.8 (413.63)	669.9 (149.94)	19.3 (4.85)
MEDIAN (MIN - MAX)	1983.2 (490 - 2081)	699.1 (8 - 887)	20.0 (4 - 27)
RELATIVE DOSE INTENSITY (%)			
>= 110%	0	4 (3.1)	6 (3.2)
>= 90%	74 (77.9)	91 (70.5)	121 (65.1)
90% TO < 110%	74 (77.9)	87 (67.4)	115 (61.8)
70% TO < 90%	19 (20.0)	31 (24.0)	52 (28.0)
50% TO < 70%	2 (2.1)	5 (3.9)	11 (5.9)
< 50%	0	2 (1.6)	1 (0.5)
NOT REPORTED	0	0	1 (0.5)

(1) Dose units: nivolumab in mg; cisplatin, docetaxel, pemetrexed, and paclitaxel in mg/ m^2, carboplatin in AUC.

Adjuvant Treatment Period

The median number of doses of adjuvant therapy (nivolumab or placebo) was the same in both arms.

Table 39. Cumulative Dose and Relative Dose Intensity of Adjuvant Therapy – All Subjects Treated with Adjuvant Therapy in the Global Population

	Arm A: Nivo + Chemo/Nivo N = 142	Arm B: Placebo + Chemo/Placebo N = 152
	Nivolumab N = 141	Placebo N = 152
NUMBER OF DOSES RECEIVED		
MEAN (SD)	10.1 (4.05)	10.7 (3.49)
MEDIAN (MIN - MAX)	13.0 (1 - 13)	13.0 (1 - 13)
CUMULATIVE DOSE (MG)		
MEAN (SD)	4857.9 (1945.10)	N.A.
MEDIAN (MIN - MAX)	6240.0 (480 - 6240)	N.A.
RELATIVE DOSE INTENSITY (%)		
>= 110%	0	N.A.
>= 90%	128 (90.8)	N.A.
90% TO < 110%	128 (90.8)	N.A.
70% TO < 90%	11 (7.8)	N.A.
50% TO < 70%	2 (1.4)	N.A.
< 50%	0	N.A.

Dose Modifications and Dose Delays

Neoadjuvant Therapy

Most subjects received 4 cycles of neoadjuvant treatment as planned. Overall, the proportions of subjects with dose modifications of chemotherapy (delay, reduction, interruption, rate reduction, omission) were similar in both treatment arms. Note that dose reductions were not permitted for nivolumab or placebo, but they were permitted for chemo.

The majority of dose delays and reductions were due to AEs. Among all treated subjects, the most frequently reported drug-related AEs of any grade leading to dose delay or reduction were as follows:

- Nivo+chemo/nivolumab arm: neutrophil count decreased/neutropenia (7.0%/4.4%) and anaemia (5.7%)
- Placebo+chemo/placebo arm: anaemia (6.5%) and neutrophil count decreased/neutropenia (6.1%/5.7%)

Table 40. Dose Modifications of Neoadjuvant Treatment – All Treated Subjects in the Global Population

	n/N Treated (%) of Subjects	
	Arm A Nivo+Chemo/Nivo (N = 228)	**Arm B Placebo+Chemo/Placebo (N = 230)**
At Least 1 Dose Delayed[a]		
Nivolumab	49/228 (21.5)	--
Placebo	--	53/230 (23.0)
Cisplatin	12/61 (19.7)	8/48 (16.7)
Docetaxel	1/11 (9.1)	2/7 (28.6)
Pemetrexed	23/104 (22.1)	23/96 (24.0)
Paclitaxel	26/117 (22.2)	26/130 (20.0)
Carboplatin	39/172 (22.7)	45/188 (23.9)
At Least 1 Dose Reduced		

	n/N Treated (%) of Subjects	
	Arm A Nivo+Chemo/Nivo (N = 228)	**Arm B Placebo+Chemo/Placebo (N = 230)**
Nivolumab	Not permitted	--
Placebo	Not permitted	--
Cisplatin	7/61 (11.5)	8/48 (16.7)
Docetaxel	4/11 (36.4)	4/7 (57.1)
Pemetrexed	6/104 (5.8)	11/96 (11.5)
Paclitaxel	24/117 (20.5)	32/130 (24.6)
Carboplatin	33/172 (19.2)	45/188 (23.9)
At Least 1 Infusion Interrupted		
Nivolumab	14/228 (6.1)	--
Placebo	--	4/230 (1.7)
Cisplatin	0/61	1/48 (2.1)
Docetaxel	2/11 (18.2)	0/7
Pemetrexed	0/104	0/96
Paclitaxel	6/117 (5.1)	11/130 (8.5)
Carboplatin	0/172	4/188 (2.1)
At Least 1 Infusion with an IV Rate Reduced		
Nivolumab	6/228 (2.6)	--
Placebo	--	0/230
Cisplatin	2/61 (3.3)	3/48 (6.3)
Docetaxel	0/11	0/7
Pemetrexed	3/104 (2.9)	2/96 (2.1)
Paclitaxel	7/117 (6.0)	9/130 (6.9)
Carboplatin	3/172 (1.7)	5/188 (2.7)
At Least 1 Omitted Dose[b]		
Nivolumab	13/228 (5.7)	--
Placebo	--	8/230 (3.5)
Cisplatin	0/61	0/48
Docetaxel	0/11	0/7
Pemetrexed	0/104	1/96 (1.0)
Paclitaxel	1/117 (0.9)	1/130 (0.8)
Carboplatin	1/172 (0.6)	1/188 (0.5)

[a] A dose was considered as actually delayed if the delay is exceeding 3 days.

[b] Omitted dose refers to a planned dose of study therapy entirely missed or withheld.

Adjuvant Therapy

In the nivo+chemo/nivolumab arm, dose delays of adjuvant therapy (nivo) were more frequent compared with placebo (placebo+chemo/placebo arm): 38.0% vs 30.9% (Table 41). AEs as a reason for dose delay were more frequently reported in subjects in the nivo+chemo/nivolumab arm compared

with the placebo+chemo/placebo arm (38.5% vs 25.6%). The proportion of subjects with a dose delay > 42 days was higher in the nivo+chemo/nivolumab arm compared with the placebo+chemo/placebo arm (11.5% vs 4.9%).

In both the nivo+chemo/nivolumab and placebo+chemo/placebo arms, infusion interruptions (1.4% vs 1.3%) and infusion rate reductions (2.1% vs 1.3%) were reported infrequently.

Table 41. Dose Delay, Infusion Interruption, and Infusion Rate Reduction for Adjuvant Therapy - All Subjects Treated with Adjuvant Therapy in the Global Population

	Arm A: Nivo + Chemo/Nivo N = 142	Arm B: Placebo + Chemo/Placebo N = 152
	Nivolumab N = 142	Placebo N = 152
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	54 (38.0)	47 (30.9)
NUMBER OF DOSES DELAYED PER SUBJECT (%)		
0	88 (62.0)	105 (69.1)
1	38 (26.8)	27 (17.8)
2	10 (7.0)	9 (5.9)
3	5 (3.5)	7 (4.6)
>= 4	1 (0.7)	4 (2.6)
TOTAL NUMBER OF DOSES DELAYED/ TOTAL NUMBER OF DOSES RECEIVED (%) (A)	78/1286 (6.1)	82/1475 (5.6)
REASON FOR DOSE DELAY (%) (B)		
ADVERSE EVENT	30 (38.5)	21 (25.6)
OTHER (C)	45 (57.7)	57 (69.5)
NOT REPORTED	3 (3.8)	4 (4.9)
LENGTH OF DOSE DELAY (%) (B)		
4 - 7 DAYS	40 (51.3)	47 (57.3)
8 - 14 DAYS	14 (17.9)	18 (22.0)
15 - 42 DAYS	15 (19.2)	13 (15.9)
> 42 DAYS	9 (11.5)	4 (4.9)
SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTED (%)	2 (1.4)	2 (1.3)
NUMBER OF INFUSIONS INTERRUPTED PER SUBJECT (%)		
0	140 (98.6)	150 (98.7)
1	2 (1.4)	2 (1.3)
2	0	0
3	0	0
>= 4	0	0
TOTAL NUMBER OF INFUSIONS INTERRUPTED/ TOTAL NUMBER OF INFUSIONS RECEIVED (%)	2/1427 (0.1)	2/1627 (0.1)
REASON FOR INFUSION INTERRUPTION (%) (D)		
HYPERSENSITIVITY REACTION	0	0
INFUSION ADMIN ISSUES	0	0
OTHER	2 (100.0)	2 (100.0)
NOT REPORTED	0	0
SUBJECTS WITH AT LEAST ONE INFUSION WITH IV RATE REDUCED (%)	3 (2.1)	2 (1.3)
NUMBER OF INFUSIONS WITH IV RATE REDUCTION PER SUBJECT (%)		
0	139 (97.9)	150 (98.7)
1	3 (2.1)	1 (0.7)
2	0	0
3	0	0
>= 4	0	1 (0.7)
TOTAL NUMBER OF IV RATES REDUCED/ TOTAL NUMBER OF DOSES RECEIVED (%)	3/1427 (0.2)	9/1627 (0.6)
REASON FOR IV RATE REDUCTION (%) (E)		

HYPERSENSITIVITY REACTION	1 (33.3)	8 (88.9)
INFUSION ADMIN ISSUES	1 (33.3)	0
OTHER	1 (33.3)	1 (11.1)
NOT REPORTED	0	0

A dose was considered as actually delayed if the delay is exceeding 3 days.

(A) Total number of doses received is excluding first dose.

(B) Percentages are computed out of the total number of doses delayed.

(C) Other reasons for dose delay were mainly due to administrative reasons or patient preference.

(D) Percentages are computed out of the total number of infusions interrupted by treatment group.

(E) Percentages are computed out of the total number of infusions with IV rate reduction by treatment group.

Definitive Surgery

After neoadjuvant treatment, most subjects in both arms were able to undergo definitive surgery (Table 16). The duration of surgery and length of hospital stay were both similar in the 2 treatment arms. A higher proportion of subjects in the nivo+chemo/nivolumab arm had clinical downstaging compared with the placebo+chemo/placebo arm.

Adverse events

Safety summary - Overall treatment period

The overall frequency of all-causality AEs was similar in the 2 treatment arms. The overall frequencies (all causality and drug-related) of SAEs and AEs leading to discontinuation were higher in the nivo+chemo/nivolumab arm than the placebo+chemo/placebo arm.

Table 42. Safety Summary - Overall Treatment Period - All Treated Subjects in the Global Population

	No. of Subjects (%)			
	Arm A Nivo+Chemo/Nivo N = 228		Arm B Placebo+Chemo/Placebo N = 230	
Deaths (includes all deaths)	40 (17.5)		48 (20.9)	
Primary Reason for Death				
Disease	21 (9.2)		39 (17.0)	
Study Drug Toxicity[a]	2 (0.9)		0	
Unknown[b]	1 (0.4)		0	
Other[c]	16 (7.0)		9 (3.9)	
	Adverse Event Grades			
Safety Parameters	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-Causality SAEs	96 (42.1)	65 (28.5)	71 (30.9)	46 (20.0)
Drug-Related SAEs	44 (19.3)	31 (13.6)	22 (9.6)	13 (5.7)
All-Causality AEs leading to DC	56 (24.6)	32 (14.0)	25 (10.9)	14 (6.1)
Drug-Related AEs leading to DC	44 (19.3)	25 (11.0)	17 (7.4)	11 (4.8)
All-Causality AEs	222 (97.4)	108 (47.4)	225 (97.8)	99 (43.0)
≥ 15% of Subjects in Any Arm, by PT				
Anaemia	90 (39.5)	18 (7.9)	74 (32.2)	10 (4.3)
Constipation	73 (32.0)	1 (0.4)	64 (27.8)	1 (0.4)
Nausea	66 (28.9)	5 (2.2)	79 (34.3)	3 (1.3)
Fatigue	64 (28.1)	7 (3.1)	60 (26.1)	3 (1.3)
Alopecia	59 (25.9)	2 (0.9)	63 (27.4)	1 (0.4)
Cough	50 (21.9)	0	46 (20.0)	0

	No. of Subjects (%)			
	Arm A Nivo+Chemo/Nivo N = 228		Arm B Placebo+Chemo/Placebo N = 230	
Decreased appetite	43 (18.9)	1 (0.4)	45 (19.6)	1 (0.4)
Neutrophil count decreased	37 (16.2)	24 (10.5)	20 (8.7)	15 (6.5)
Dyspnoea	36 (15.8)	4 (1.8)	35 (15.2)	2 (0.9)
Diarrhoea	34 (14.9)	2 (0.9)	35 (15.2)	1 (0.4)
Arthralgia	43 (18.9)	4 (1.8)	41 (17.8)	1 (0.4)
Drug-Related AEs	203 (89.0)	74 (32.5)	200 (87.0)	58 (25.2)
≥ 15% of Subjects in Any Arm, by PT				
Anaemia	57 (25.0)	8 (3.5)	51 (22.2)	8 (3.5)
Nausea	53 (23.2)	2 (0.9)	65 (28.3)	3 (1.3)
Alopecia	52 (22.8)	1 (0.4)	53 (23.0)	0
Constipation	51 (22.4)	0	39 (17.0)	1 (0.4)
Fatigue	47 (20.6)	5 (2.2)	44 (19.1)	2 (0.9)
Neutrophil count decreased	35 (15.4)	23 (10.1)	20 (8.7)	15 (6.5)
All-causality Select AEs, by Category				
Endocrine	42 (18.4)	2 (0.9)	13 (15.7)	0
Gastrointestinal	37 (16.2)	6 (2.6)	37 (16.1)	2 (0.9)
Hepatic	46 (20.2)	5 (2.2)	31 (13.5)	3 (1.3)
Pulmonary	17 (7.5)	4 (1.8)	8 (3.5)	5 (2.2)
Renal	34 (14.9)	3 (1.3)	18 (7.8)	1 (0.4)
Skin	71 (31.1)	3 (1.3)	53 (23.0)	0
Hypersensitivity/Infusion Reactions	15 (6.6)	2 (0.9)	14 (6.1)	3 (1.3)
Drug-Related Select AEs, by Category				
Endocrine	33 (14.5)	1 (0.4)	12 (5.2)	0
Gastrointestinal	28 (12.3)	5 (2.2)	20 (8.7)	1 (0.4)
Hepatic	30 (13.2)	3 (1.3)	20 (8.7)	2 (0.9)
Pulmonary	14 (6.1)	3 (1.3)	3 (1.3)	2 (0.9)
Renal	26 (11.4)	2 (0.9)	10 (4.3)	1 (0.4)
Skin	54 (23.7)	3 (1.3)	34 (14.8)	0
Hypersensitivity/Infusion Reactions	14 (6.1)	2 (0.9)	11 (4.8)	3 (1.3)
All-causality IMAEs within 100 Days of Last Dose Treated with Immune Modulating Medication, by Category				
Diarrhoea/Colitis	5 (2.2)	2 (0.9)	2 (0.9)	0
Hepatitis	0	0	1 (0.4)	0
Pneumonitis	12 (5.3)	5 (2.2)	3 (1.3)	2 (0.9)
Nephritis/Renal Dysfunction	7 (3.1)	3 (1.3)	0	0
Rash	11 (4.8)	2 (0.9)	2 (0.9)	0
Hypersensitivity/Infusion Reactions	1 (0.4)	0	0	0
All-causality Endocrine IMAEs within 100 Days of Last Dose With or Without Immune Modulating Medication, by Category				
Adrenal Insufficiency	4 (1.8)	0	0	0
Hypophysitis	2 (0.9)	0	1 (0.4)	1 (0.4)
Hypothyroidism/Thyroiditis	25 (11.0)	0	4 (1.7)	0
Hyperthyroidism	11 (4.8)	1 (0.4)	5 (2.2)	0
Diabetes Mellitus	2 (0.9)	0	0	0
All-causality OESIs within 100 Days of Last Dose With or Without Immune Modulating Medication, by Category[d]				
Pancreatitis	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Myositis/Rhabdomyolysis	2 (0.9)	2 (0.9)	0	0
Guillain-Barre Syndrome	1 (0.4)	0	0	0

	No. of Subjects (%)			
	Arm A Nivo+Chemo/Nivo N = 228		Arm B Placebo+Chemo/Placebo N = 230	
Myocarditis	1 (0.4)	1 (0.4)	0	0

[a] In both subjects, the cause of death per investigator was pneumonitis.

[b] The subject died at home and communication with family was unsuccessful.

[c] The verbatim terms reported for the 'other' reasons for death are provided in the CA20977T CSR[1], and were consistent with events anticipated in the study population. None were considered related to study drug (per the investigator).

[d] No OESIs were reported in the following categories: encephalitis, myasthenic syndrome, demyelination, uveitis, or graft versus host disease.

MedDRA version 26.0; CTCAE version 4.0.

Includes events reported between first treatment and 30 days after last treatment of study therapy (unless otherwise indicated) including definitive surgery and radiotherapy, unless otherwise indicated.

All-Causality Adverse Events

Table 43. Adverse Events by Worst CTC Grade Reported in ≥10% of All Treated Subjects in the Global Population

System Organ Class (%) Preferred Term (%)	Arm A: Nivo + Chemo / Nivo N = 228			Arm B: Placebo + Chemo / Placebo N = 230		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	222 (97.4)	108 (47.4)	7 (3.1)	225 (97.8)	99 (43.0)	4 (1.7)
Gastrointestinal disorders	141 (61.8)	13 (5.7)	0	147 (63.9)	8 (3.5)	0
Constipation	73 (32.0)	1 (0.4)	0	64 (27.8)	1 (0.4)	0
Nausea	66 (28.9)	5 (2.2)	0	79 (34.3)	3 (1.3)	0
Diarrhoea	34 (14.9)	2 (0.9)	0	35 (15.2)	1 (0.4)	0
Vomiting	26 (11.4)	4 (1.8)	0	24 (10.4)	1 (0.4)	0
General disorders and administration site conditions	129 (56.6)	11 (4.8)	1 (0.4)	118 (51.3)	9 (3.9)	0
Fatigue	64 (28.1)	7 (3.1)	0	60 (26.1)	3 (1.3)	0
Pyrexia	25 (11.0)	1 (0.4)	0	14 (6.1)	0	0
Asthenia	22 (9.6)	1 (0.4)	0	26 (11.3)	2 (0.9)	0
Skin and subcutaneous tissue disorders	118 (51.8)	6 (2.6)	0	109 (47.4)	2 (0.9)	0
Alopecia	59 (25.9)	2 (0.9)	0	63 (27.4)	1 (0.4)	0
Pruritus	32 (14.0)	1 (0.4)	0	16 (7.0)	0	0
Rash	26 (11.4)	1 (0.4)	0	27 (11.7)	0	0
Respiratory, thoracic and mediastinal disorders	114 (50.0)	20 (8.8)	1 (0.4)	117 (50.9)	20 (8.7)	2 (0.9)
Cough	50 (21.9)	0	0	46 (20.0)	0	0
Dyspnoea	36 (15.8)	4 (1.8)	0	35 (15.2)	2 (0.9)	0
Investigations	111 (48.7)	34 (14.9)	0	79 (34.3)	21 (9.1)	0
Neutrophil count decreased	37 (16.2)	24 (10.5)	0	20 (8.7)	15 (6.5)	0
Blood creatinine increased	29 (12.7)	0	0	12 (5.2)	0	0
White blood cell count decreased	28 (12.3)	13 (5.7)	0	10 (4.3)	3 (1.3)	0
Alanine aminotransferase increased	25 (11.0)	3 (1.3)	0	14 (6.1)	1 (0.4)	0
Blood and lymphatic system disorders	109 (47.8)	27 (11.8)	0	95 (41.3)	26 (11.3)	0
Anaemia	90 (39.5)	18 (7.9)	0	74 (32.2)	10 (4.3)	0
Neutropenia	24 (10.5)	8 (3.5)	0	23 (10.0)	13 (5.7)	0
Nervous system disorders	108 (47.4)	9 (3.9)	1 (0.4)	108 (47.0)	9 (3.9)	0
Peripheral sensory neuropathy	29 (12.7)	1 (0.4)	0	23 (10.0)	0	0
Neuropathy peripheral	24 (10.5)	1 (0.4)	0	25 (10.9)	2 (0.9)	0
Infections and infestations	97 (42.5)	26 (11.4)	1 (0.4)	90 (39.1)	16 (7.0)	1 (0.4)
COVID-19	26 (11.4)	2 (0.9)	0	23 (10.0)	2 (0.9)	0
Musculoskeletal and connective tissue disorders	93 (40.8)	10 (4.4)	0	96 (41.7)	2 (0.9)	0
Arthralgia	43 (18.9)	4 (1.8)	0	41 (17.8)	1 (0.4)	0
Myalgia	17 (7.5)	1 (0.4)	0	24 (10.4)	0	0
Metabolism and nutrition disorders	88 (38.6)	17 (7.5)	0	88 (38.3)	12 (5.2)	0
Decreased appetite	43 (18.9)	1 (0.4)	0	45 (19.6)	1 (0.4)	0

Endocrine disorders	39 (17.1)	2 (0.9)	0	11 (4.8)	0	0
Hypothyroidism	25 (11.0)	0	0	4 (1.7)	0	0

MedDRA Version: 26.0; CTC Version: 4.0

Includes events reported between first treatment and 30 days after last treatment of study therapy including definitive surgery and radiotherapy.

Drug-Related Adverse Events

Nivo+chemo/nivolumab arm: The most frequently reported drug-related AEs (all grades, PTs) were anaemia (25.0%), nausea (23.2%), and alopecia (22.8%). The most frequently reported drug-related Grade 3/4 AEs (PTs) were neutrophil count decreased (10.1%), WBC decreased (5.7%), and anaemia (3.5%).

- Placebo+chemo/placebo arm: The most frequently reported drug-related AEs (all grades, PTs) were nausea (28.3%), alopecia (23.0%), and anaemia (22.2%). The most frequently reported drug-related Grade 3/4 AEs (PTs) were neutrophil count decreased (6.5%), neutropenia (5.7%), and anaemia (3.5%).

Table 44. Drug-Related Adverse Events by Worst CTC Grade Reported in ≥5% of All Treated Subjects - All Treated Subjects - All Treated Subjects in the Global Population

System Organ Class (%) Preferred Term (%)	Arm A: Nivo + Chemo/Nivo N = 228			Arm B: Placebo + Chemo/Placebo N = 230		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	203 (89.0)	74 (32.5)	1 (0.4)	200 (87.0)	58 (25.2)	0
Gastrointestinal disorders	109 (47.8)	6 (2.6)	0	104 (45.2)	5 (2.2)	0
Nausea	53 (23.2)	2 (0.9)	0	65 (28.3)	3 (1.3)	0
Constipation	51 (22.4)	0	0	39 (17.0)	1 (0.4)	0
Diarrhoea	26 (11.4)	2 (0.9)	0	19 (8.3)	0	0
Vomiting	17 (7.5)	2 (0.9)	0	17 (7.4)	1 (0.4)	0
Skin and subcutaneous tissue disorders	98 (43.0)	5 (2.2)	0	77 (33.5)	0	0
Alopecia	52 (22.8)	1 (0.4)	0	53 (23.0)	0	0
Pruritus	20 (8.8)	1 (0.4)	0	10 (4.3)	0	0
Rash	20 (8.8)	1 (0.4)	0	15 (6.5)	0	0
Rash maculo-papular	13 (5.7)	1 (0.4)	0	4 (1.7)	0	0
General disorders and administration site conditions	88 (38.6)	6 (2.6)	0	80 (34.8)	4 (1.7)	0
Fatigue	47 (20.6)	5 (2.2)	0	44 (19.1)	2 (0.9)	0
Asthenia	18 (7.9)	1 (0.4)	0	21 (9.1)	2 (0.9)	0

Malaise	11 (4.8)	0	0	15 (6.5)	0	0
Investigations	85 (37.3)	28 (12.3)	0	52 (22.6)	19 (8.3)	0
Neutrophil count decreased	35 (15.4)	23 (10.1)	0	20 (8.7)	15 (6.5)	0
White blood cell count decreased	25 (11.0)	13 (5.7)	0	10 (4.3)	2 (0.9)	0
Blood creatinine increased	22 (9.6)	0	0	6 (2.6)	0	0
Alanine aminotransferase increased	19 (8.3)	2 (0.9)	0	9 (3.9)	1 (0.4)	0
Platelet count decreased	15 (6.6)	3 (1.3)	0	15 (6.5)	2 (0.9)	0
Blood and lymphatic system disorders	76 (33.3)	17 (7.5)	0	70 (30.4)	24 (10.4)	0
Anaemia	57 (25.0)	8 (3.5)	0	51 (22.2)	8 (3.5)	0
Neutropenia	21 (9.2)	7 (3.1)	0	22 (9.6)	13 (5.7)	0
Leukopenia	5 (2.2)	0	0	13 (5.7)	2 (0.9)	0
Nervous system disorders	72 (31.6)	3 (1.3)	0	81 (35.2)	2 (0.9)	0
Peripheral sensory neuropathy	26 (11.4)	1 (0.4)	0	18 (7.8)	0	0
Neuropathy peripheral	18 (7.9)	0	0	20 (8.7)	2 (0.9)	0
Dysgeusia	7 (3.1)	0	0	13 (5.7)	0	0
Metabolism and nutrition disorders	48 (21.1)	7 (3.1)	0	39 (17.0)	5 (2.2)	0
Decreased appetite	31 (13.6)	0	0	29 (12.6)	1 (0.4)	0
Musculoskeletal and connective tissue disorders	43 (18.9)	6 (2.6)	0	46 (20.0)	2 (0.9)	0
Arthralgia	26 (11.4)	3 (1.3)	0	25 (10.9)	1 (0.4)	0
Myalgia	14 (6.1)	1 (0.4)	0	18 (7.8)	0	0
Respiratory, thoracic, and mediastinal disorders	36 (15.8)	3 (1.3)	1 (0.4)	28 (12.2)	2 (0.9)	0
Hiccups	16 (7.0)	0	0	10 (4.3)	0	0
Endocrine disorders	33 (14.5)	1 (0.4)	0	9 (3.9)	0	0
Hypothyroidism	19 (8.3)	0	0	4 (1.7)	0	0
Hyperthyroidism	13 (5.7)	1 (0.4)	0	4 (1.7)	0	0

MedDRA Version: 26.0 CTC Version: 4.0

Includes events reported between first treatment and 30 days after last treatment of study therapy including definitive surgery and radiotherapy.

AEs Due to COVID-19

There were 37 (16.2%) subjects in the nivo+chemo/nivolumab arm and 27 (11.7%) subjects in the placebo+chemo/placebo arm that had AEs due to COVID-19 reported between first treatment and 100 days after last treatment of study therapy including definitive surgery and PORT.

2 subjects in the nivo+chemo/nivolumab arm died due to a COVID-19 infection; these deaths were not considered by the investigator to be related to any study drug. No subjects in the placebo+chemo/placebo arm died due to a COVID-19 infection.

Safety summary in the neoadjuvant treatment period

Table 45. Overall Safety - Neoadjuvant Period - All Treated Subjects in the Global Population

	No. of Subjects (%)			
	Arm A Nivo+Chemo/Nivo N = 228		Arm B Placebo+Chemo/Placebo N = 230	
Deaths (from the start of neoadjuvant therapy to the last dose of neoadjuvant therapy + 30 days)	5 (2.2)		4 (1.7)	
Primary Reason for Death				
Disease	1 (0.4)		0	
Study Drug Toxicity[a]	1 (0.4)		0	
Unknown	0		0	
Other[b]	3 (1.3)		4 (1.7)	
All-causality SAEs	48 (21.1)	33 (14.5)	34 (14.8)	19 (8.3)
Drug-related SAEs	32 (14.0)	23 (10.1)	19 (8.3)	11 (4.8)
All-causality AEs leading to DC	30 (13.2)	20 (8.8)	16 (7.0)	10 (4.3)
Drug-Related AEs leading to DC	26 (11.4)	17 (7.5)	12 (5.2)	9 (3.9)
All-Causality AEs	216 (94.7)	78 (34.2)	221 (96.1)	63 (27.4)
≥ 15% of Subjects in Any Arm, by PT				
Anaemia	75 (32.9)	11 (4.8)	61 (26.5)	8 (3.5)
Constipation	64 (28.1)	1 (0.4)	55 (23.9)	1 (0.4)
Alopecia	59 (25.9)	2 (0.9)	62 (27.0)	1 (0.4)
Nausea	58 (25.4)	3 (1.3)	69 (30.0)	3 (1.3)
Fatigue	54 (23.7)	4 (1.8)	54 (23.5)	2 (0.9)
Decreased appetite	36 (15.8)	0	33 (14.3)	1 (0.4)
Neutrophil count decreased	36 (15.8)	23 (10.1)	20 (8.7)	15 (6.5)
Drug-Related AEs	197 (86.4)	62 (27.2)	195 (84.8)	52 (22.6)
≥ 15% of Subjects in Any Arm, by PT				
Nausea	52 (22.8)	1 (0.4)	60 (26.1)	3 (1.3)
Alopecia	52 (22.8)	1 (0.4)	52 (22.6)	0
Constipation	50 (21.9)	0	37 (16.1)	1 (0.4)
Anaemia	50 (21.9)	6 (2.6)	46 (20.0)	6 (2.6)
Fatigue	43 (18.9)	4 (1.8)	40 (17.4)	2 (0.9)

	No. of Subjects (%)			
	Arm A Nivo+Chemo/Nivo N = 228		Arm B Placebo+Chemo/Placebo N = 230	
All-Causality Select AEs, by Category				
Endocrine	14 (6.1)	2 (0.9)	7 (3.0)	0
Gastrointestinal	24 (10.5)	3 (1.3)	27 (11.7)	1 (0.4)
Hepatic	27 (11.8)	4 (1.8)	18 (7.8)	1 (0.4)
Pulmonary	8 (3.5)	2 (0.9)	0	0
Renal	19 (8.3)	1 (0.4)	10 (4.3)	1 (0.4)
Skin	51 (22.4)	2 (0.9)	42 (18.3)	0
Hypersensitivity	14 (6.1)	2 (0.9)	10 (4.3)	3 (1.3)
Drug-Related Select AEs, by Category				
Endocrine	11 (4.8)	1 (0.4)	6 (2.6)	0
Gastrointestinal	21 (9.2)	3 (1.3)	19 (8.3)	1 (0.4)
Hepatic	20 (8.8)	3 (1.3)	14 (6.1)	1 (0.4)
Pulmonary	7 (3.1)	2 (0.9)	0	0
Renal	15 (6.6)	1 (0.4)	6 (2.6)	1 (0.4)
Skin	39 (17.1)	2 (0.9)	30 (13.0)	0
Hypersensitivity	14 (6.1)	2 (0.9)	10 (4.3)	3 (1.3)
All-causality IMAEs within 100 Days of Last Dose Treated with Immune Modulating Medication, by Category				
Diarrhoea/Colitis	2 (0.9)	1 (0.4)	0	0
Hepatitis	0	0	1 (0.4)	0
Pneumonitis	6 (2.6)	4 (1.8)	2 (0.9)	2 (0.9)
Nephritis/Renal Dysfunction	4 (1.8)	2 (0.9)	0	0
Rash	8 (3.5)	2 (0.9)	2 (0.9)	0
Hypersensitivity	1 (0.4)	0	0	0
All-causality Endocrine IMAEs within 100 Days of Last Dose With or Without Immune Modulating Medication, by Category				
Hypophysitis	2 (0.9)	0	1 (0.4)	1 (0.4)
Hypothyroidism/Thyroiditis	9 (3.9)	0	3 (1.3)	0
Hyperthyroidism	10 (4.4)	1 (0.4)	2 (0.9)	0
Diabetes Mellitus	1 (0.4)	0	0	0
All-causality OESIs within 100 Days of Last Dose With or Without Immune Modulating Medication, by Category[c]				
Pancreatitis	1 (0.4)	1 (0.4)	0	0
Myositis/Rhabdomyolysis	2 (0.9)	2 (0.9)	0	0
Guillain-Barre Syndrome	1 (0.4)	0	0	0
Myocarditis	1 (0.4)	1 (0.4)	0	0

[a] The cause of death per investigator was pneumonitis. There was another death due to study drug toxicity (pneumonitis) in the nivo+chemo/nivo arm; this death occurred > 100 days after the last dose of neoadjuvant study drug.

[b] The verbatim terms reported for the 'other' reasons for death are provided in the CSR, and were consistent with events anticipated in the study population. None were considered related to study drug (per the investigator).

[c] No OESIs were reported in the following categories: encephalitis, myasthenic syndrome, demyelination, uveitis, or graft versus host disease.

MedDRA version 26.0; CTCAE version 4.0.

Safety summary related to surgery

Table 46. Adverse Events Leading to Surgical Delay or Cancellation and AEs Identified as Surgical complications – All Treated Subjects in the Global Population

	No. of Subjects (%)			
	Arm A Nivo+Chemo/Nivo N = 228		Arm B Placebo+Chemo/Placebo N = 230	
Safety Parameters	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality AEs leading to surgical delay	8 (3.5)	2 (0.9)	5 (2.2)	1 (0.4)
All-causality AEs leading to surgery cancellation	7 (3.1)	3 (1.3)	4 (1.7)	1 (0.4)
All Treated Subjects in the Global Population with Surgery	**N = 178**		**N = 178**	
AEs identified as surgical complications[a]	73 (41.0)	21 (11.8)	69 (38.8)	21 (11.8)
SAEs identified as surgical complications[a]	23 (12.9)	14 (7.9)	20 (11.2)	16 (9.0)

[a] Includes the period from the date of definitive surgery through 90 days after definitive surgery or through the initiation of adjuvant therapy, whichever was earlier.

Safety summary – Adjuvant period

Table 47. Overall Safety - Adjuvant Period - All Treated Subjects in the Global Population Who Received Adjuvant Therapy

	No. of Subjects (%)			
	Arm A Nivo+Chemo/Nivo N = 142		Arm B Placebo+Chemo/Placebo N = 152	
Deaths (from the start of adjuvant therapy to the last dose of adjuvant therapy + 30 days)	0		0	
	Adverse Event Grades			
Safety Parameters	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	31 (21.8)	19 (13.4)	23 (15.1)	14 (9.2)
Drug-related SAEs	10 (7.0)	5 (3.5)	2 (1.3)	1 (0.7)
All-causality AEs leading to DC	20 (14.1)	7 (4.9)	7 (4.6)	1 (0.7)
Drug-Related AEs leading to DC	14 (9.9)	6 (4.2)	4 (2.6)	0

	No. of Subjects (%)			
	Arm A Nivo+Chemo/Nivo N = 142		Arm B Placebo+Chemo/Placebo N = 152	
All-Causality AEs	124 (87.3)	28 (19.7)	121 (79.6)	23 (15.1)
≥ 10% of Subjects in Any Arm, by PT				
Cough	24 (16.9)	0	15 (9.9)	0
COVID-19	19 (13.4)	1 (0.7)	16 (10.5)	0
Pruritus	18 (12.7)	1 (0.7)	3 (2.0)	0
Anaemia	17 (12.0)	0	8 (5.3)	0
Drug-Related AEs	71 (50.0)	12 (8.5)	45 (29.6)	4 (2.6)
≥ 5% of Subjects in Any Arm, by PT				
Pruritus	11 (7.7)	1 (0.7)	2 (1.3)	0
Hypothyroidism	10 (7.0)	0	0	0
Anaemia	8 (5.6)	0	0	0
All-Causality Select AEs, by Category				
Endocrine	21 (14.8)	0	4 (2.6)	0
Gastrointestinal	13 (9.2)	2 (1.4)	9 (5.9)	0
Hepatic	15 (10.6)	0	9 (5.9)	2 (1.3)
Pulmonary	9 (6.3)	1 (0.7)	1 (0.7)	0
Renal	10 (7.0)	0	6 (3.9)	0
Skin	25 (17.6)	1 (0.7)	13 (8.6)	0
Hypersensitivity/Infusion Reactions	0	0	3 (2.0)	0
Drug-Related Select AEs, by Category				
Endocrine	16 (11.3)	0	4 (2.6)	0
Gastrointestinal	9 (6.3)	2 (1.4)	1 (0.7)	0
Hepatic	4 (2.8)	0	4 (2.6)	1 (0.7)
Pulmonary	8 (5.6)	1 (0.7)	1 (0.7)	0
Renal	6 (4.2)	0	4 (2.6)	0
Skin	17 (12.0)	1 (0.7)	5 (3.3)	0
Hypersensitivity/Infusion Reactions	0	0	1 (0.7)	0
All-causality IMAEs within 100 Days of Last Dose Treated with Immune Modulating Medication, by Category				
Diarrhoea/Colitis	3 (2.1)	1 (0.7)	2 (1.3)	0
Pneumonitis	6 (4.2)	1 (0.7)	1 (0.7)	0
Nephritis/Renal Dysfunction	2 (1.4)	0	0	0
Rash	3 (2.1)	0	0	0

	No. of Subjects (%)			
	Arm A Nivo+Chemo/Nivo N = 142		Arm B Placebo+Chemo/Placebo N = 152	
All-causality Endocrine IMAEs within 100 Days of Last Dose With or Without Immune Modulating Medication, by Category				
Adrenal Insufficiency	3 (2.1)	0	0	0
Hypothyroidism/Thyroiditis	13 (9.2)	0	1 (0.7)	0
Hyperthyroidism	0	0	3 (2.0)	0
Diabetes Mellitus	1 (0.7)	0	0	0
All-causality OESIs within 100 Days of Last Dose With or Without Immune Modulating Medication, by Category[a]				
Pancreatitis	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)

[a] No OESIs were reported in the following categories: encephalitis, myositis/rhabdomyolysis, myasthenic syndrome, demyelination, Guillain-Barre Syndrome, uveitis, myocarditis, or graft versus host disease.

MedDRA version 26.0; CTCAE version 4.0.

Includes events reported between first dose of adjuvant therapy through 30 days (or 100 days, as applicable) after the last dose of adjuvant therapy

Updated safety data

During the procedure, the MAH provided an updated safety analysis based on the 22-Mar-2024 clinical data cutoff and 26-Apr-2024 DBL.

Table 48. Updated Safety Summary During the Overall Treatment Period - All Treated Subjects - Based on the 26-Apr-2024 DBL

	No. of Subjects (%)			
	Arm A Nivo+Chemo/Nivo N = 228		Arm B Placebo+Chemo/Placebo N = 230	
Deaths (includes all deaths)	55 (24.1)		64 (27.8)	
Primary Reason for Death				
Disease	31 (13.6)		53 (23.0)	
Study Drug Toxicity[a]	2 (0.9)		0	
Unknown[b]	2 (0.9)		0	
Other[c]	20 (8.8)		11 (4.8)	
	Adverse Event Grades			
Safety Parameters	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade3-4**
All-Causality SAEs	96 (42.1)	65 (28.5)	71 (30.9)	46 (20.0)
Drug-Related SAEs	43 (18.9)	31 (13.6)	22 (9.6)	13 (5.7)
All-Causality AEs leading to DC	57 (25.0)	32 (14.0)	25 (10.9)	14 (6.1)
All-Causality AEs	222 (97.4)	107 (46.9)	225 (97.8)	98 (42.6)
≥ 15% of Subjects in Any Arm, by PT				
Anaemia	90 (39.5)	18 (7.9)	74 (32.2)	10 (4.3)
Constipation	73 (32.0)	1 (0.4)	64 (27.8)	1 (0.4)
Nausea	66 (28.9)	5 (2.2)	79 (34.3)	3 (1.3)
Fatigue	64 (28.1)	7 (3.1)	60 (26.1)	3 (1.3)
Alopecia	59 (25.9)	0	63 (27.4)	0
Cough	51 (22.4)	0	46 (20.0)	0
Decreased appetite	43 (18.9)	1 (0.4)	45 (19.6)	1 (0.4)
Neutrophil count decreased	37 (16.2)	24 (10.5)	20 (8.7)	15 (6.5)
Dyspnoea	36 (15.8)	4 (1.8)	35 (15.2)	2 (0.9)

	No. of Subjects (%)			
	Arm A Nivo+Chemo/Nivo N = 228		Arm B Placebo+Chemo/Placebo N = 230	
Diarrhoea	34 (14.9)	2 (0.9)	35 (15.2)	1 (0.4)
Arthralgia	44 (19.3)	4 (1.8)	42 (18.3)	1 (0.4)
Drug-Related AEs	203 (89.0)	73 (32.0)	200 (87.0)	58 (25.2)
≥ 15% of Subjects in Any Arm, by PT				
Anaemia	57 (25.0)	8 (3.5)	51 (22.2)	8 (3.5)
Nausea	53 (23.2)	2 (0.9)	65 (28.3)	3 (1.3)
Alopecia	52 (22.8)	1 (0.4)	53 (23.0)	0
Constipation	51 (22.4)	0	39 (17.0)	1 (0.4)
Fatigue	47 (20.6)	5 (2.2)	44 (19.1)	2 (0.9)
Neutrophil count decreased	35 (15.4)	23 (10.1)	20 (8.7)	15 (6.5)
	Adverse Event Grades			
Safety Parameters	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality IMAEs within 100 Days of Last Dose Treated with Immune Modulating Medication, by Category				
Diarrhoea/Colitis	5 (2.2)	2 (0.9)	2 (0.9)	0
Hepatitis	0	0	1 (0.4)	0
Pneumonitis	12 (5.3)	5 (2.2)	3 (1.3)	2 (0.9)
Nephritis/Renal Dysfunction	7 (3.1)	3 (1.3)	0	0
Rash	11 (4.8)	2 (0.9)	2 (0.9)	0
Hypersensitivity/Infusion Reactions	1 (0.4)	0	0	0
All-causality Endocrine IMAEs within 100 Days of Last Dose With or Without Immune Modulating Medication, by Category				
Adrenal Insufficiency	4 (1.8)	0	0	0
Hypophysitis	2 (0.9)	0	1 (0.4)	1 (0.4)
Hypothyroidism/Thyroiditis	25 (11.0)	0	4 (1.7)	0
Hyperthyroidism	11 (4.8)	1 (0.4)	5 (2.2)	0
Diabetes Mellitus	2 (0.9)	0	0	0
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade3-4**
All Treated Subjects with Surgery	**N = 178**		**N = 178**	
All-causality AEs identified as surgical complications[d]	73 (41.0)	21 (11.8)	69 (38.8)	21 (11.8)

[a] In both subjects, the cause of death per investigator was pneumonitis.

[b] One subject died at home and communication with family was unsuccessful. Another subject (per the latest DBL) died during the survival follow-up (death certificate is pending at site).

[c] The verbatim terms reported for the 'other' reasons for death were as follows in each arm (Appendix 16.2.7.4 [death listing] in Attachment Q16):

Nivo+chemo/nivolumab (n=20): Malignant neoplasm progression, septic shock, cerebrovascular accident, haemoptysis, COVID-19 (2 subjects), cardiac arrest, pneumonia, post procedural haemorrhage, ischemic stroke, acute myocardial infarction, sudden death, died in sleep, cerebral infarction with lung cancer as the background, pneumonia pseudomonal, ventilator associated pneumonia. 4 new deaths reported per the latest DBL were pulmonary embolism; possible haemorrhage from internal organs (occurred approximately 2 yrs after last dose), but no autopsy was performed, and the cause is unknown; disease progression; asphyxiation by coughing up blood.

Placebo+chemo/placebo (n=11): Cardio-respiratory arrest, pneumothorax, respiratory failure, chronic respiratory failure, gastrointestinal perforation, pneumonia (2 subjects), diarrhoea and hypovolemic shock, complication from idiopathic pulmonary fibrosis. 2 new deaths reported per the latest DBL were acute myocardial infarction and stroke.

The verbatim terms reported for the 'other' reasons for death were consistent with events anticipated in the study population. None were considered related to study drug (per the investigator).

[d] Includes the period from the date of definitive surgery through 90 days after definitive surgery or through the initiation of adjuvant therapy, whichever was earlier.

MedDRA version 26.1; CTCAE version 4.0.

Includes events reported between first treatment and 30 days after last treatment of study therapy (unless otherwise indicated) including definitive surgery and radiotherapy, unless otherwise indicated.

Adverse drug reactions

Per EMA guidance documents and in line with the pooling strategy of procedure Opdivo II/0096 previously agreed upon with the CHMP, a Pooled Nivolumab + Chemotherapy dataset was created using the data from all treated subjects in the Nivolumab + Chemo arms in the following studies:

Table 49. List of Studies for the Integrated Safety Analysis with Nivo+Chemo (N = 1800 Patients)

Study (Database Lock), Number of Nivo+Chemo Subjects Included	Tumour Indications			
	ESCC	GC/GEJ/EAC	UC	NSCLC
CA209648 (Oct-2021), n = 310	X			
CA209649 (Jul-2020), n = 782		X		
CA209901 (Jun-2023), n = 304			X	
CA209816 (Oct-2022), n = 176				X
CA20977T (Apr-2024), n = 228				X

Abbreviations: ESCC: oesophageal squamous cell carcinoma; GC = gastric cancer; GEJ: gastroesophageal junction; EAC: oesophageal adenocarcinoma; UC: urothelial carcinoma; NSCLC: non-small cell lung cancer.

No new ADRs have been identified, however, some incidences have been updated as a result of the updated pool (see Table below), update of the PI was based on the safety DCO of 22-Mar-2024 for study CA20977T.

Table 50. Summary of Any Adverse Events using Re-mapped Terms Occurring in > 10% of Subjects in the Pool - All Nivolumab + Chemotherapy Treated Subjects from CA20977T and Pooled Including CA20977T

System Organ Class (%)	CA20977T Nivolumab + Chemotherapy N = 228		Pooled Nivolumab + Chemotherapy Including CA20977T N = 1800	
Preferred Term (%)	Any Grade	Grade 3-4	Any Grade	Grade 3-4
TOTAL SUBJECTS WITH AN EVENT	**222 (97.4)**	**107 (46.9)**	**1774 (98.6)**	**1169 (64.9)**
Gastrointestinal disorders	**143 (62.7)**	**13 (5.7)**	**1409 (78.3)**	**328 (18.2)**
Nausea	66 (28.9)	5 (2.2)	867 (48.2)	45 (2.5)
Constipation	73 (32.0)	1 (0.4)	552 (30.7)	9 (0.5)
Diarrhoea	34 (14.9)	2 (0.9)	507 (28.2)	58 (3.2)
Vomiting	26 (11.4)	4 (1.8)	432 (24.0)	50 (2.8)
Abdominal pain	17 (7.5)	1 (0.4)	320 (17.8)	30 (1.7)
Stomatitis	15 (6.6)	0	315 (17.5)	43 (2.4)
Blood and lymphatic system disorders	**129 (56.6)**	**48 (21.1)**	**1253 (69.6)**	**662 (36.8)**
Anaemia	91 (39.9)	18 (7.9)	803 (44.6)	244 (13.6)
Neutropenia	61 (26.8)	32 (14.0)	754 (41.9)	433 (24.1)
Thrombocytopenia	28 (12.3)	3 (1.3)	526 (29.2)	104 (5.8)
General disorders and administration site conditions	**127 (55.7)**	**11 (4.8)**	**1126 (62.6)**	**134 (7.4)**
Fatigue	85 (37.3)	7 (3.1)	721 (40.1)	91 (5.1)
Pyrexia	25 (11.0)	1 (0.4)	285 (15.8)	13 (0.7)
Oedema	18 (7.9)	0	224 (12.4)	4 (0.2)

System Organ Class (%)	CA20977T Nivolumab + Chemotherapy N = 228		Pooled Nivolumab + Chemotherapy Including CA20977T N = 1800	
Preferred Term (%)	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Metabolism and nutrition disorders	**89 (39.0)**	**19 (8.3)**	**979 (54.4)**	**256 (14.2)**
Decreased appetite	43 (18.9)	1 (0.4)	553 (30.7)	57 (3.2)
Investigations	**96 (42.1)**	**19 (8.3)**	**918 (51.0)**	**257 (14.3)**
Transaminases increased	30 (13.2)	3 (1.3)	297 (16.5)	39 (2.2)
White blood cell count decreased	28 (12.3)	13 (5.7)	274 (15.2)	87 (4.8)
Weight decreased	13 (5.7)	0	224 (12.4)	13 (0.7)
Blood creatinine increased	29 (12.7)	0	185 (10.3)	8 (0.4)
Nervous system disorders	**110 (48.2)**	**9 (3.9)**	**907 (50.4)**	**128 (7.1)**
Neuropathy peripheral	61 (26.8)	3 (1.3)	597 (33.2)	63 (3.5)
Skin and subcutaneous tissue disorders	**119 (52.2)**	**4 (1.8)**	**753 (41.8)**	**50 (2.8)**
Rash	43 (18.9)	2 (0.9)	337 (18.7)	28 (1.6)
Pruritus	32 (14.0)	1 (0.4)	200 (11.1)	4 (0.2)
Respiratory, thoracic and mediastinal disorders	**115 (50.4)**	**20 (8.8)**	**678 (37.7)**	**109 (6.1)**
Cough	53 (23.2)	0	242 (13.4)	2 (0.1)
Musculoskeletal and connective tissue disorders	**93 (40.8)**	**10 (4.4)**	**512 (28.4)**	**41 (2.3)**
Musculoskeletal pain	49 (21.5)	2 (0.9)	325 (18.1)	22 (1.2)

MedDRA Version: 26.1; CTC Version 4.0

For CA20977T study, includes events reported between first dose and last dose of therapy including definitive surgery and radiotherapy + 30 days. For other studies included in the pool, includes events reported between first dose and 30 days after last dose of study therapy.

Some preferred terms are re-mapped based on BMS medical review.

Nivolumab + Chemotherapy Pooled groups consist of nivolumab + chemotherapy treatment group from studies CA209648, CA209649, CA209901, CA209816 and CA20977T

In addition, the adverse reactions by decreased frequency were aligned within each System Organ Class in the column "Combination with chemotherapy (See Table 9 of section 4.8 of the SmPC). Further to the updated safety pool, 2 ADRs frequencies were updated as follows:

Hypoalbuminaemia: from very common to common.

Guillain Barré syndrome: from rare to uncommon.

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

The overall frequency reported for all-causality and drug-related SAEs were higher in the nivo+chemo/nivolumab arm than the placebo+chemo/placebo arm (Table 51).

Table 51. Serious Adverse Events by Worst CTC Grade Reported in at Least 2 Subjects During the Overall Treatment Period - All Treated Subjects in the Global Population

System Organ Class (%) Preferred Term (%)	Arm A: Nivo + Chemo/Nivo N = 228			Arm B: Placebo + Chemo/Placebo N = 230		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	96 (42.1)	65 (28.5)	7 (3.1)	71 (30.9)	46 (20.0)	4 (1.7)
Infections and infestations	28 (12.3)	23 (10.1)	1 (0.4)	22 (9.6)	13 (5.7)	1 (0.4)
Pneumonia	8 (3.5)	7 (3.1)	0	9 (3.9)	4 (1.7)	1 (0.4)
Sepsis	3 (1.3)	3 (1.3)	0	0	0	0
COVID-19	2 (0.9)	2 (0.9)	0	2 (0.9)	2 (0.9)	0
Gastroenteritis	2 (0.9)	1 (0.4)	0	0	0	0
COVID-19 pneumonia	0	0	0	2 (0.9)	1 (0.4)	0
Infectious pleural effusion	0	0	0	2 (0.9)	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	27 (11.8)	16 (7.0)	1 (0.4)	22 (9.6)	17 (7.4)	2 (0.9)
Haemoptysis	5 (2.2)	2 (0.9)	0	1 (0.4)	1 (0.4)	0
Pneumonitis (A)	5 (2.2)	2 (0.9)	1 (0.4)	4 (1.7)	4 (1.7)	0
Hypoxia	3 (1.3)	2 (0.9)	0	1 (0.4)	1 (0.4)	0
Dyspnoea	1 (0.4)	1 (0.4)	0	3 (1.3)	2 (0.9)	0
Pleural effusion	1 (0.4)	1 (0.4)	0	3 (1.3)	2 (0.9)	0
Pulmonary embolism	1 (0.4)	1 (0.4)	0	2 (0.9)	1 (0.4)	0
Gastrointestinal disorders	22 (9.6)	11 (4.8)	0	7 (3.0)	5 (2.2)	0
Colitis	3 (1.3)	1 (0.4)	0	0	0	0
Gastritis	2 (0.9)	0	0	0	0	0
Nausea	2 (0.9)	2 (0.9)	0	3 (1.3)	2 (0.9)	0
Vomiting	2 (0.9)	2 (0.9)	0	1 (0.4)	1 (0.4)	0
General disorders and administration site conditions	8 (3.5)	3 (1.3)	1 (0.4)	5 (2.2)	2 (0.9)	0
General physical health deterioration	2 (0.9)	2 (0.9)	0	0	0	0
Pyrexia	2 (0.9)	1 (0.4)	0	1 (0.4)	0	0
Asthenia	0	0	0	2 (0.9)	1 (0.4)	0
Fatigue	0	0	0	2 (0.9)	1 (0.4)	0
Nervous system disorders	7 (3.1)	4 (1.8)	1 (0.4)	3 (1.3)	3 (1.3)	0
Cerebrovascular accident	2 (0.9)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0
Blood and lymphatic system disorders	6 (2.6)	4 (1.8)	0	6 (2.6)	3 (1.3)	0
Febrile neutropenia	2 (0.9)	2 (0.9)	0	0	0	0
Anaemia	1 (0.4)	0	0	4 (1.7)	2 (0.9)	0
Neutropenia	1 (0.4)	1 (0.4)	0	2 (0.9)	1 (0.4)	0
Hepatobiliary disorders	5 (2.2)	5 (2.2)	0	0	0	0

Cholecystitis acute	2 (0.9)	2 (0.9)	0	0	0	0

System Organ Class (%) Preferred Term (%)	Arm A: Nivo + Chemo/Nivo N = 228			Arm B: Placebo + Chemo/Placebo N = 230		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Cardiac disorders	4 (1.8)	2 (0.9)	1 (0.4)	6 (2.6)	3 (1.3)	1 (0.4)
Atrial fibrillation	1 (0.4)	0	0	4 (1.7)	3 (1.3)	0
Investigations	4 (1.8)	4 (1.8)	0	6 (2.6)	1 (0.4)	0
Neutrophil count decreased	3 (1.3)	3 (1.3)	0	1 (0.4)	1 (0.4)	0
Platelet count decreased	0	0	0	3 (1.3)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.8)	1 (0.4)	1 (0.4)	7 (3.0)	4 (1.7)	0
Malignant neoplasm progression	2 (0.9)	1 (0.4)	1 (0.4)	4 (1.7)	2 (0.9)	0
Metastases to central nervous system	0	0	0	2 (0.9)	1 (0.4)	0
Renal and urinary disorders	4 (1.8)	3 (1.3)	0	1 (0.4)	1 (0.4)	0
Acute kidney injury	4 (1.8)	3 (1.3)	0	0	0	0
Metabolism and nutrition disorders	3 (1.3)	1 (0.4)	0	5 (2.2)	4 (1.7)	0
Hyperglycaemia	2 (0.9)	1 (0.4)	0	0	0	0
Dehydration	0	0	0	2 (0.9)	2 (0.9)	0
Hyponatremia	0	0	0	2 (0.9)	2 (0.9)	0

(A) There was an additional death due to pneumonitis in the nivo+chemo/nivo arm; this death occurred > 100 days after the last dose of neoadjuvant study drug.

MedDRA Version: 26.0; CTC Version: 4.0

Includes events reported between first treatment and 30 days after last treatment of study therapy including definitive surgery and radiotherapy.

Deaths

A total of 40 (17.5%) subjects and 48 (20.9%) subjects in the nivo+chemo/nivolumab and placebo+chemo/placebo arms died, respectively (Table 52). Disease progression was the most frequently reported cause of death in both arms. An additional 23 and 37 subjects in the nivo+chemo/nivolumab arm and placebo+chemo/placebo arm, respectively, died after the extended follow-up safety window (>100 days after the last treatment of study therapy).

Table 52. Death Summary During the Overall Treatment Period

	Arm A: Nivolumab + Chemo/Nivolumab N = 228	Arm B Placebo + Chemo/Placebo N = 230
NUMBER OF SUBJECTS WHO DIED (%)	40 (17.5)	48 (20.9)
PRIMARY REASON FOR DEATH (%)		
DISEASE	21 (9.2)	39 (17.0)
STUDY DRUG TOXICITY	2 (0.9)	0
UNKNOWN	1 (0.4)	0
OTHER (a)	16 (7.0)	9 (3.9)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST TREATMENT OF STUDY THERAPY (%)	9 (3.9)	4 (1.7)
PRIMARY REASON FOR DEATH (%)		
DISEASE	1 (0.4)	0
STUDY DRUG TOXICITY	1 (0.4)	0
UNKNOWN	0	0
OTHER (a)	7 (3.1)	4 (1.7)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST TREATMENT OF STUDY THERAPY (%)	17 (7.5)	11 (4.8)
PRIMARY REASON FOR DEATH (%)		
DISEASE	3 (1.3)	4 (1.7)
STUDY DRUG TOXICITY	1 (0.4)	0
UNKNOWN	1 (0.4)	0
OTHER (a)	12 (5.3)	7 (3.0)

(a) Verbatim terms for deaths attributed to "other" are listed in CA20977T Primary CSR.

Deaths due to study drug toxicity were reported in two subjects (0.9%) in the nivo+chemo/nivolumab arm, and both were due to pneumonitis. Both subjects died after completing 4 cycles of neoadjuvant treatment but before surgery. One of these deaths occurred 28 days after the last dose of nivolumab, whereas the other death occurred 154 days after the last dose of nivolumab.

No deaths in the placebo+chemo/placebo arm were reported as due to study drug toxicity (per the investigator).

One death was reported with reason recorded as unknown. This subject died at home 101 days after the 4th dose of nivolumab (neoadjuvant phase) and 72 days after surgery. However, no information could be gathered regarding the cause of death (or autopsy report if any).

Deaths due to 'other' reasons were reported for 16 (7.0%) subjects in the nivo+chemo/nivolumab arm and 9 (3.9%) subjects in the placebo+chemo/placebo arm. The verbatim terms reported for the 'other' reasons for death in treated subjects are provided in the table below.

Table 53: Verbatim Terms for Deaths Attributed to "Other" - All Treated Subjects in the Global Population

Arm A Nivo+Chemo/Nivo	Arm B Placebo+Chemo/Placebo
Verbatim Term	Verbatim Term
Malignant neoplasm progression	Cardio-respiratory arrest
Septic shock	Pneumothorax

Arm A Nivo+Chemo/Nivo	Arm B Placebo+Chemo/Placebo
Verbatim Term	**Verbatim Term**
Cerebrovascular accident	Respiratory failure
Haemoptysis	Chronic respiratory failure
COVID-19	Gastrointestinal perforation
Cardiac arrest	Pneumonia
Pneumonia	Diarrhoea and Hypovolemic shock
Post procedural haemorrhage	“Complication from idiopathic pulmonary fibrosis”
Ischemic stroke	Pneumonia
COVID-19	
Acute myocardial infarction	
Sudden death	
“Died in sleep”	
“Cerebral infarction with lung cancer as the background”	
Pneumonia pseudomonal	
“Ventilator associated pneumonia”	

Deaths following surgery were reported in a lower proportion of subjects in the nivo+chemo/nivolumab arm than in the placebo+chemo/placebo arm.

- Nivo+chemo/nivolumab arm: 4 subjects died within 90 days of surgery; the reported causes of death included septic shock, post procedural haemorrhage, acute myocardial infarction, and unknown. None of these deaths were considered to be related to study drug (study drug toxicity) per the investigator.
- Placebo+chemo/placebo arm: 1 subject died within 90 days of surgery; the reported cause of death was pneumonia that was not considered to be related to study drug per the investigator.

Table 54. Deaths After Surgery - All Treated Subjects with Surgery in the Global Population

	Arm A: Nivo + Chemo/Nivo N = 178	Arm B Placebo + Chemo/Placebo N = 178
NUMBER OF SUBJECTS WHO DIED (%)	18 (10.1)	26 (14.6)
PRIMARY REASON FOR DEATH (%)		
DISEASE	6 (3.4)	22 (12.4)
STUDY DRUG TOXICITY	0	0
UNKNOWN	1 (0.6)	0
OTHER	11 (6.2)	4 (2.2)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF SURGERY (%)	3 (1.7)	1 (0.6)
PRIMARY REASON FOR DEATH (%)		
DISEASE	0	0
STUDY DRUG TOXICITY	0	0
UNKNOWN	0	0
OTHER	3 (1.7)	1 (0.6)
NUMBER OF SUBJECTS WHO DIED WITHIN 90 DAYS OF SURGERY (%)	4 (2.2)	1 (0.6)
PRIMARY REASON FOR DEATH (%)		
DISEASE	0	0
STUDY DRUG TOXICITY	0	0
UNKNOWN	1 (0.6)	0
OTHER	3 (1.7)	1 (0.6)

AEs leading to death

Table 55. Any Adverse Events Leading to Death on Overall Treatment Summary by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) All Treated Subjects in Global Population

System Organ Class (%) Preferred Term (%)	Arm A: Nivo + Chemo / Nivo N = 228			Arm B: Placebo + Chemo / Placebo N = 230		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	16 (7.0)	4 (1.8)	12 (5.3)	12 (5.2)	2 (0.9)	9 (3.9)
Infections and infestations	5 (2.2)	3 (1.3)	2 (0.9)	2 (0.9)	0	2 (0.9)
COVID-19	2 (0.9)	2 (0.9)	0	0	0	0
Pneumonia	1 (0.4)	0	1 (0.4)	2 (0.9)	0	2 (0.9)
Pneumonia pseudomonal	1 (0.4)	1 (0.4)	0	0	0	0
Septic shock	1 (0.4)	0	1 (0.4)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.3)	0	3 (1.3)	3 (1.3)	1 (0.4)	1 (0.4)
Malignant neoplasm progression	3 (1.3)	0	3 (1.3)	3 (1.3)	1 (0.4)	1 (0.4)
Cardiac disorders	2 (0.9)	0	2 (0.9)	1 (0.4)	0	1 (0.4)
Acute myocardial infarction	1 (0.4)	0	1 (0.4)	0	0	0
Cardiac arrest	1 (0.4)	0	1 (0.4)	0	0	0
Cardio-respiratory arrest	0	0	0	1 (0.4)	0	1 (0.4)
General disorders and administration site conditions	2 (0.9)	0	2 (0.9)	0	0	0
Death	1 (0.4)	0	1 (0.4)	0	0	0
Sudden death	1 (0.4)	0	1 (0.4)	0	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.9)	1 (0.4)	1 (0.4)	4 (1.7)	1 (0.4)	3 (1.3)
Haemoptysis	1 (0.4)	1 (0.4)	0	1 (0.4)	0	1 (0.4)
Pneumonitis	1 (0.4)	0	1 (0.4)	0	0	0
Chronic respiratory failure	0	0	0	1 (0.4)	0	1 (0.4)
Pneumothorax	0	0	0	1 (0.4)	1 (0.4)	0
Respiratory failure	0	0	0	1 (0.4)	0	1 (0.4)
Injury, poisoning and procedural complications	1 (0.4)	0	1 (0.4)	0	0	0
Post procedural haemorrhage	1 (0.4)	0	1 (0.4)	0	0	0
Nervous system disorders	1 (0.4)	0	1 (0.4)	0	0	0
Cerebrovascular accident	1 (0.4)	0	1 (0.4)	0	0	0
Gastrointestinal disorders	0	0	0	2 (0.9)	1 (0.4)	1 (0.4)
Diarrhoea	0	0	0	1 (0.4)	1 (0.4)	0
Gastrointestinal perforation	0	0	0	1 (0.4)	0	1 (0.4)
Vascular disorders	0	0	0	1 (0.4)	0	1 (0.4)
Hypovolaemic shock	0	0	0	1 (0.4)	0	1 (0.4)

MedDRA Version: 26.0
CTC Version: 4.0
Includes events reported between first treatment and 100 days after last treatment of study therapy including definitive surgery and radiotherapy.
AEs with Leading to Death: AEs with an AE grade 5 and/or an AE outcome='Fatal'
Program Source: /opt/zfs002/prd/bms251840/stats/primary/prog/tables/rt-ae-aecat-sas.sas 28SEP2023:10:35:21

Select adverse events

Select AEs were more frequently reported with nivo+chemo/nivolumab compared with placebo+chemo/placebo but were infrequent and mostly Grade 1-2 (Table 42).

The most frequently reported drug-related select AE categories (all grades were as follows):

– Nivo+chemo/nivolumab arm: skin (23.7%), endocrine (14.5%), and hepatic (13.2%)

– Placebo+chemo/placebo arm: skin (14.8%), GI and hepatic (8.7% each)

The most frequently reported drug-related select AEs by PT (all grades) were as follows:

– Nivo+chemo/nivolumab arm: diarrhoea (11.4%), blood creatinine increased (9.6%), pruritus and rash (8.8% each).

– Placebo+chemo/placebo: diarrhoea (8.3%), rash (6.5%), AST increased and pruritus (4.3% each)

Drug-related serious select AEs were infrequently reported (≤ 3.1% by category) in both treatment arms.

The majority of select AEs were considered drug related by the investigator.

Table 56. Onset, Management, and Resolution of Drug-Related Select AEs during the Overall Treatment Period - All Treated Subjects in the Nivo+Chemo/Nivolumab Arm (N = 228) in the Global Population

Category	N (%) Treated Subj. with Any Grade/ Grade 3-4 Drug-related Select AE	Median Time to Onset of Drug-related Select AE (range), wks	% Treated Subj. with Drug-related Select AE Leading to DC	% Subj. with Drug-Related Select AE Treated with IMM / High-dose Corticosteroids[a]	Median Time[b] to Resolution of Drug-related Select AE (range), wks[c,d,e]	% Subj. with Drug-related Select AE that Resolved[d,e]
Endocrine	33 (14.5)/ 1 (0.4)	20.86 (5.7 - 62.7)	0.4	12.1 / 0	22.29 (0.3+ - 140.1+)	57.6
Gastrointestinal	28 (12.3)/ 5 (2.2)	3.79 (0.3 - 67.3)	1.8	14.3 / 14.3	1.07 (0.3 - 28.1)	100
Hepatic	30 (13.2)/ 3 (1.3)	3.71 (0.6 - 55.9)	0	0 / 0	5.71 (0.6 - 123.3+)	90.0
Pulmonary	14 (6.1)/ 3 (1.3)	21.14 (0.6 - 63.4)	3.9	78.6 / 64.3	11.57 (0.4 - 136.9+)	71.4
Renal	26 (11.4)/ 2 (0.9)	5.93 (0.4 - 59.6)	1.3	19.2 / 19.2	4.71 (0.3 - 92.1+)	84.6
Skin	54 (23.7)/ 3 (1.3)	4.29 (0.1 - 61.0)	0.9	37.0 / 7.4	10.07 (0.1 - 117.4+)	85.2
Hypersensitivity/ Infusion Reaction	14 (6.1)/ 2 (0.9)	3.00 (0.1 - 6.6)	0.4	35.7 / 14.3	0.14 (0.1 - 11.0)	100

[a] Denominator is based on the number of subjects who experienced the event

[b] From Kaplan-Meier estimation.

[c] Symbol + indicates a censored value.

[d] Subjects who experienced select adverse event without worsening from baseline grade were excluded from time to resolution analysis.

[e] Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved.

MedDRA Version: 26.0, CTC Version 4.0

Includes events reported between first treatment and 30 days after last treatment of study therapy including definitive surgery and radiotherapy.

These outputs also include Grade 3-5 and chemotherapy results.

Immune-mediated adverse events (IMAEs)

Across IMAE categories, the majority of events in the nivo+chemo/nivolumab arm were manageable using the established management algorithms, with resolution reported when IMMs (mostly systemic corticosteroids) were administered (Table 57). The category with the most unresolved events was endocrine IMAEs; this was due to the continuing need for hormone replacement therapy.

Table 57. Onset, Management, and Resolution of All-Causality IMAEs within 100 days of Last Dose - All Treated Subjects in the Nivo+Chemo/Nivolumab Arm (N = 228) in the Global Population

IMAE Category	N (%) Subj. with Any Grade/ Grade 3-4 IMAEs	Median Time to IMAE Onset (range), wks	% Subj. with IMAE leading to DC / Dose Delay	% Subj. with IMAEs Receiving IMM / High-dose Corticosteroids[a]	Median Duration IMM (range), wks	% Subj. with Resolution of IMAE[b,c]	Median[d] Time to Resolution (range), wks[b,c]
Pneumonitis	12 (5.3)/ 5 (2.2)	25.93 (9.7 - 63.4)	4.4 / 0.4	100 / 75.0	7.79 (3.3 - 85.6)	58.3	14.00 (0.4 - 128.9+)
Diarrhoea/Colitis	5 (2.2)/ 2 (0.9)	31.57 (2.9 - 52.9)	1.8 / 0	100 / 80.0	13.29 (2.0 - 61.0)	80.0	22.43 (0.4 - 30.3+)
Hepatitis	0/0	NA	0 / 0	0 / 0	NA	0	NA
Nephritis/Renal Dysfunction	7 (3.1)/ 3 (1.3)	25.00 (4.1 - 59.6)	1.3 / 0.9	100 / 100	6.43 (3.1 - 72.4)	71.4	13.14 (3.1 - 74.3+)
Rash	11 (4.8)/ 2 (0.9)	2.43 (1.1 - 57.3)	0.9 / 0.4	100 / 45.5	22.14 (1.1 - 113.0)	90.9	12.86 (1.1 - 92.0+)
Hypersensitivity	1 (0.4)/ 0	6.00 (6.0 - 6.0)	0 / 0	100 / 0	0.14 (0.1 - 0.1)	100	0.14 (0.1 - 0.1)
Adrenal Insufficiency	4 (1.8)/ 0	30.29 (26.9 - 34.1)	0 / 0.4	100 / 25.0	3.86 (2.1 - 115.3)	25.0	NA (3.0 - 115.3+)
Hypothyroidism/ Thyroiditis	25 (11.0)/ 0	25.00 (8.1 - 75.3)	0.4 / 1.3	0 / 0	NA	44.0	105.14 (1.3 - 140.1+)
Diabetes Mellitus	2 (0.9)/ 0	22.93 (22.7 - 23.1)	0 / 0	0 / 0	NA	50.0	NA (8.7 - 106.1+)
Hyperthyroidism	11 (4.8)/ 1 (0.4)	10.14 (5.7 - 28.4)	0.4 / 0	18.2 / 0	5.86 (2.7 - 9.0)	100	9.57 (2.1 - 19.4)
Hypophysitis	2 (0.9)/ 0	17.79 (12.4 - 23.1)	0.4 / 0	50.0 / 50.0	8.29 (8.3 - 8.3)	50.0	NA (8.7 - 95.9+)

[a] Denominator is based on the number of subjects who experienced the event.

[b] Subjects who experienced IMAE without worsening from baseline grade were excluded from time to resolution analysis.

[c] Events without a stop date or with a stop date equal to the death as well as Grade 5 events are considered unresolved.

[d] From Kaplan-Meier estimation. Note that the number of events was very low for most categories.

Symbol + indicates a censored value.

MedDRA Version: 26.0, CTC Version 4.0

Includes events reported between first treatment and 100 days after last treatment of study therapy including definitive surgery and radiotherapy.

These outputs also include Grade 3-5 and chemotherapy results.

Other events of special interest (OESIs)

Seven OESIs (all causality, with or without IMM treatment) were reported with extended follow-up.

Most subjects with OESIs were treated with IMMs and the majority of OESIs resolved (4 of the 6 events in the nivo+chemo/nivolumab arm and the 1 event in the placebo+chemo/placebo arm resolved. No OESIs were Grade 5.

Surgical complications

The proportions of subjects with AEs and SAEs identified as surgical complications by the investigator (occurring up to 90 days after definitive surgery) were similar in the 2 treatment arms.

Table 58. All-Causality Adverse Events Reported During the Overall Treatment Period as Surgical Complications by Worst CTC Grade Occurring in at Least 2 Subjects - All Treated Subjects in the Global Population with Definitive Surgery

System Organ Class (%) Preferred Term (%)	Arm A: Nivo + Chemo/Nivo N = 178			Arm B: Placebo + Chemo/Placebo N = 178		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	73 (41.0)	21 (11.8)	3 (1.7)	69 (38.8)	21 (11.8)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	32 (18.0)	10 (5.6)	0	31 (17.4)	11 (6.2)	0
Dyspnoea	9 (5.1)	2 (1.1)	0	11 (6.2)	0	0
Pneumothorax	7 (3.9)	1 (0.6)	0	5 (2.8)	2 (1.1)	0
Cough	6 (3.4)	0	0	5 (2.8)	0	0
Hypoxia	6 (3.4)	2 (1.1)	0	1 (0.6)	0	0
Pleural effusion	5 (2.8)	1 (0.6)	0	8 (4.5)	2 (1.1)	0
Dysphonia	2 (1.1)	0	0	3 (1.7)	0	0
Emphysema	2 (1.1)	0	0	0	0	0
Pulmonary fistula	2 (1.1)	2 (1.1)	0	0	0	0
Atelectasis	1 (0.6)	0	0	3 (1.7)	2 (1.1)	0
Pneumonitis	0	0	0	3 (1.7)	2 (1.1)	0
Injury, poisoning and procedural complications	30 (16.9)	4 (2.2)	1 (0.6)	21 (11.8)	3 (1.7)	0
Incision site pain	11 (6.2)	2 (1.1)	0	12 (6.7)	2 (1.1)	0
Procedural pain	10 (5.6)	1 (0.6)	0	3 (1.7)	0	0
Wound complication	5 (2.8)	0	0	3 (1.7)	0	0
Procedural haemorrhage	2 (1.1)	1 (0.6)	0	0	0	0
Wound dehiscence	1 (0.6)	0	0	2 (1.1)	1 (0.6)	0
Seroma	0	0	0	2 (1.1)	0	0
Infections and infestations	13 (7.3)	4 (2.2)	1 (0.6)	9 (5.1)	5 (2.8)	1 (0.6)
Pneumonia	4 (2.2)	1 (0.6)	0	3 (1.7)	1 (0.6)	1 (0.6)
Wound infection	2 (1.1)	0	0	0	0	0
Empyema	0	0	0	2 (1.1)	2 (1.1)	0
Blood and lymphatic system disorders	12 (6.7)	4 (2.2)	0	5 (2.8)	1 (0.6)	0
Anaemia	9 (5.1)	4 (2.2)	0	5 (2.8)	1 (0.6)	0
Iron deficiency anaemia	2 (1.1)	0	0	0	0	0

Gastrointestinal disorders	10 (5.6)	1 (0.6)	0	5 (2.8)	1 (0.6)	0
Constipation	5 (2.8)	0	0	2 (1.1)	0	0
Nausea	3 (1.7)	0	0	2 (1.1)	0	0
General disorders and administration site conditions	9 (5.1)	0	0	20 (11.2)	2 (1.1)	0
Pain	3 (1.7)	0	0	3 (1.7)	0	0
Fatigue	2 (1.1)	0	0	2 (1.1)	0	0
Chest pain	1 (0.6)	0	0	5 (2.8)	1 (0.6)	0
Non-cardiac chest pain	1 (0.6)	0	0	6 (3.4)	0	0
Pyrexia	1 (0.6)	0	0	2 (1.1)	0	0
Musculoskeletal and connective tissue disorders	9 (5.1)	1 (0.6)	0	6 (3.4)	0	0
Musculoskeletal chest pain	7 (3.9)	1 (0.6)	0	4 (2.2)	0	0
Cardiac disorders	7 (3.9)	0	1 (0.6)	8 (4.5)	1 (0.6)	0
Atrial fibrillation	5 (2.8)	0	0	6 (3.4)	1 (0.6)	0
Skin and subcutaneous tissue disorders	6 (3.4)	0	0	4 (2.2)	1 (0.6)	0
Subcutaneous emphysema	4 (2.2)	0	0	3 (1.7)	1 (0.6)	0
Metabolism and nutrition disorders	5 (2.8)	2 (1.1)	0	6 (3.4)	0	0
Hypoalbuminaemia	1 (0.6)	0	0	2 (1.1)	0	0
Hypoproteinaemia	0	0	0	2 (1.1)	0	0
Nervous system disorders	5 (2.8)	1 (0.6)	0	3 (1.7)	0	0
Intercostal neuralgia	2 (1.1)	0	0	1 (0.6)	0	0
Vascular disorders	4 (2.2)	1 (0.6)	0	3 (1.7)	2 (1.1)	0
Embolism	2 (1.1)	0	0	0	0	0
Hypertension	1 (0.6)	0	0	2 (1.1)	1 (0.6)	0
Hypotension	0	0	0	2 (1.1)	1 (0.6)	0
Investigations	3 (1.7)	0	0	3 (1.7)	0	0
White blood cell count increased	0	0	0	2 (1.1)	0	0

MedDRA Version: 26.0. CTC Version: 4.0

Includes events reported up to 90 days after definitive surgery.

Immunogenicity

The highest titer value observed in nivolumab ADA positive subjects was 128, which occurred in 2 subjects. All other titers were low, ranging from 1 to 128. ADA Assessments Summary is summarised in Table 4 above.

Of the nivo+chemo/nivo-treated subjects evaluable for ADA, a small proportion of both nivolumab ADA-positive and nivolumab ADA-negative subjects had select AEs of hypersensitivity or infusion reaction, with most hypersensitivity or infusion reactions reported in ADA negative subjects .

Table 59. Select Adverse Events of Hypersensitivity/Infusion Reaction by ADA Status (Positive, Negative) - All Nivo+Chemo/Nivo-Treated Subjects in the Global Population

	Arm A: Nivo + Chemo/Nivo	
Preferred Term (%)	Nivolumab ADA Positive N = 24	Nivolumab ADA Negative N = 174
TOTAL SUBJECTS WITH AN EVENT	1 (4.2)	13 (7.5)
Anaphylactic reaction	0	1 (0.6)
Hypersensitivity	1 (4.2)	3 (1.7)
Infusion related hypersensitivity reaction	0	1 (0.6)
Infusion related reaction	0	9 (5.2)

MedDRA Version: 26.0; CTC Version: 4.0

Includes events between first treatment and within the last treatment of study therapy including definitive surgery and radiotherapy + 100 days.

Laboratory findings

Laboratory abnormalities (haematology, liver tests, kidney function tests, thyroid function tests, and electrolytes) were primarily Grade 1-2 in severity (Table 60).

Table 60. On-Treatment Worst CTC Grade Laboratory Parameters that Worsened Relative to Baseline within 30 Days Follow-up (SI Units) - All Treated Subjects in the Global Population

	Arm A: Nivolumab + Chemo / Nivolumab N = 228			Arm B: Placebo + Chemo / Placebo N = 230		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
HEMOGLOBIN (B)	223	169 (75.8)	16 (7.2)	226	152 (67.3)	14 (6.2)
PLATELET COUNT	223	74 (33.2)	3 (1.3)	226	85 (37.6)	5 (2.2)
LEUKOCYTES, LOCAL LAB	223	90 (40.4)	19 (8.5)	226	77 (34.1)	7 (3.1)
LYMPHOCYTES (ABSOLUTE), TOTAL	223	103 (46.2)	15 (6.7)	226	79 (35.0)	11 (4.9)
ABSOLUTE NEUTROPHIL COUNT	223	117 (52.5)	39 (17.5)	226	97 (42.9)	33 (14.6)
ALKALINE PHOSPHATASE , LOCAL LAB	223	55 (24.7)	0	225	51 (22.7)	0
ASPARTATE AMINOTRANSFERASE, LOCAL LAB	223	73 (32.7)	6 (2.7)	225	50 (22.2)	1 (0.4)
ALANINE AMINOTRANSFERASE, LOCAL LAB	223	81 (36.3)	5 (2.2)	224	52 (23.2)	1 (0.4)
BILIRUBIN, TOTAL, LOCAL LAB	221	17 (7.7)	2 (0.9)	224	10 (4.5)	0
CREATININE, LOCAL LAB	223	75 (33.6)	1 (0.4)	226	58 (25.7)	0
PHOSPHATE, LOCAL LAB	219	34 (15.5)	6 (2.7)	221	46 (20.8)	5 (2.3)
HYPERNATREMIA	223	7 (3.1)	0	226	16 (7.1)	0
HYPONATREMIA	223	60 (26.9)	7 (3.1)	226	52 (23.0)	5 (2.2)
HYPERKALEMIA	223	62 (27.8)	3 (1.3)	226	45 (19.9)	2 (0.9)
HYPOKALEMIA	223	25 (11.2)	3 (1.3)	226	28 (12.4)	2 (0.9)

HYPERCALCEMIA	222	35 (15.8)	1 (0.5)	224	33 (14.7)	0
HYPOCALCEMIA	222	38 (17.1)	3 (1.4)	224	46 (20.5)	2 (0.9)
HYPERGLYCEMIA	114	49 (43.0)	6 (5.3)	116	53 (45.7)	1 (0.9)
HYPOGLYCEMIA	223	12 (5.4)	1 (0.4)	225	16 (7.1)	1 (0.4)

Toxicity Scale: CTC version 4.0
Includes laboratory results reported between first treatment and last treatment of study therapy + 30 days
(A) N: Subjects with a CTC Graded Laboratory Result for the given parameter from both Baseline and On-treatment. Percentages are based on N as denominator.
(B) Per Anaemia criteria in CTC version 4.0 there is no grade 4 for haemoglobin.

Abnormalities in haematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2 (Table 60). Hematologic parameters that worsened to Grade 3-4 from baseline (in ≥5% of subjects) were as follows:

- Nivo+chemo/nivolumab arm: decreased absolute neutrophil count (17.5%), decreased leukocytes (8.5%), decreased haemoglobin (7.2%), and decreased lymphocytes (6.7%)
- Placebo+chemo/placebo arm: decreased absolute neutrophil count (14.6%), and decreased haemoglobin (6.2%)

Abnormalities in liver function tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2. Liver function tests (AST, ALT, ALP, total bilirubin) that worsened from baseline to Grade 3-4 during the treatment period or within 30 days of last dose of study drug were as follows:

- Nivo+chemo/nivolumab arm: increased AST (2.7%), increased ALT (2.2%), and increased bilirubin (0.9%)
- Placebo+chemo/placebo arm: increased AST and increased ALT (0.4% each)

Two subjects in the nivo+chemo/nivolumab arm were reported with concurrent ALT or AST > 3 x ULN with total bilirubin > 2 x ULN within 30 days of last dose of study therapy (Table 61).

Table 61. On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units) - All Treated Subjects in the Global Population

Abnormality (%)	Arm A: Nivolumab + Chemo/Nivolumab N = 228	Arm B: Placebo + Chemo/Placebo N = 230
	N = 223	N = 226
ALT OR AST > 3XULN	15 (6.7)	10 (4.4)
ALT OR AST > 5XULN	7 (3.1)	1 (0.4)
ALT OR AST > 10XULN	3 (1.3)	1 (0.4)
ALT OR AST > 20XULN	1 (0.4)	0
	N = 223	N = 225
TOTAL BILIRUBIN > 2XULN	2 (0.9)	0
ALP > 1.5XULN	24 (10.8)	24 (10.7)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN ONE DAY	3 (1.3)	0
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN 30 DAYS	3 (1.3)	0
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	2 (0.9)	0
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	2 (0.9)	0

Includes laboratory results reported after the first treatment and within 30 days of last treatment of study therapy including definitive surgery and radiotherapy.
Denominator corresponds to subjects with at least 1 on-treatment measurement of the corresponding laboratory parameter.

Regarding kidney function tests, most subjects had normal creatinine values during the treatment reporting period. All abnormalities in creatinine (increases) were Grade 1 or 2 except for 1 Grade 4 event reported in subject CA20977T-2-688 the nivo+chemo/nivolumab arm.

Regarding thyroid function tests, TSH increases to > ULN from a baseline level ≤ ULN were reported in 23.1% and 9.8% of subjects in the nivo+chemo/nivolumab and placebo+chemo/placebo arms, respectively. Decreases to < LLN from a baseline level ≥LLN were reported in 17.6% and 12.1% of subjects in the nivo+chemo/nivolumab and placebo+chemo/placebo arms, respectively.

Table 62. On-Treatment Laboratory Abnormalities in Specific Thyroid Tests (SI Units) - All Treated Subjects with at Least One On-Treatment TSH Measurement in the Global Population

Abnormality (%)	Arm A: Nivo + Chemo/Nivo N = 221	Arm B: Placebo + Chemo/Placebo N = 224
TSH > ULN	62 (28.1)	30 (13.4)
TSH > ULN WITH TSH <= ULN AT BASELINE	51 (23.1)	22 (9.8)
TSH > ULN WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	22 (10.0)	7 (3.1)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	47 (21.3)	22 (9.8)
WITH FT3/FT4 TEST MISSING (A) (B)	13 (5.9)	12 (5.4)
TSH < LLN	51 (23.1)	42 (18.8)
TSH < LLN WITH TSH >= LLN AT BASELINE	39 (17.6)	27 (12.1)
TSH < LLN WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	27 (12.2)	11 (4.9)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	35 (15.8)	37 (16.5)
WITH FT3/FT4 TEST MISSING (A) (B)	6 (2.7)	7 (3.1)

Includes laboratory results reported after the first treatment and within 30 days of last treatment of study therapy including definitive surgery and radiotherapy.

(A) Within a 2-week window after the abnormal TSH test date.

(B) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.

Most subjects had normal electrolyte levels during the treatment period; abnormalities in electrolytes during treatment were primarily Grade 1-2.

Most subjects had normal glucose levels during the treatment period; abnormalities in glucose during treatment were primarily Grade 1-2. In both treatment arms, a small proportion of subjects (≤ 5.3%) had increases in glucose levels (hyperglycaemia) that worsened from baseline to Grade 3/4 during the treatment period or within 30 days of last dose of study drug.

Safety related to drug-drug interactions and other interactions

No formal pharmacokinetic drug interaction studies have been conducted with nivolumab, therefore no new information has been generated in support of this submission.

Safety in special populations

The frequencies of AEs (all causality and drug-related) for subgroups of age, sex, race, and region, were generally consistent with the corresponding frequencies reported for the overall study population

by treatment arm. However, in both arms, the frequencies of Grade 3-4 AEs (all-causality or drug-related) were numerically higher in some subgroups compared with the corresponding frequencies reported for the overall study population by treatment arm. In both arms, the frequencies of drug-related Grade 3-4 AEs were higher in Asian subjects compared with the overall study population by treatment arm.

Table 63. All-Causality AEs during the Overall Treatment Period by Worst CTC Grade and by Age, Sex, Race, Region, and Type of Platinum Therapy - All Treated Subjects in the Global Population

	Arm A: Nivo + Chemo / Nivo N = 228				Arm B: Placebo + Chemo / Placebo N = 230			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
OVERALL STUDY POPULATION	**228**	**222 (97.4)**	**108 (47.4)**	**7 (3.1)**	**230**	**225 (97.8)**	**99 (43.0)**	**4 (1.7)**
SEX (%)								
MALE	167	165 (98.8)	80 (47.9)	5 (3.0)	158	154 (97.5)	71 (44.9)	4 (2.5)
FEMALE	61	57 (93.4)	28 (45.9)	2 (3.3)	72	71 (98.6)	28 (38.9)	0
RACE (%)								
WHITE	154	148 (96.1)	66 (42.9)	6 (3.9)	174	170 (97.7)	72 (41.4)	3 (1.7)
BLACK OR AFRICAN AMERICAN	4	4 (100.0)	2 (50.0)	0	4	4 (100.0)	0	0
ASIAN	66	66 (100.0)	38 (57.6)	1 (1.5)	49	48 (98.0)	27 (55.1)	1 (2.0)
OTHER	4	4 (100.0)	2 (50.0)	0	3	3 (100.0)	0	0
AGE (%)								
< 65	102	99 (97.1)	49 (48.0)	2 (2.0)	100	99 (99.0)	35 (35.0)	1 (1.0)
>= 65 AND < 75	114	111 (97.4)	54 (47.4)	5 (4.4)	112	108 (96.4)	55 (49.1)	2 (1.8)
>= 75	12	12 (100.0)	5 (41.7)	0	18	18 (100.0)	9 (50.0)	1 (5.6)
>= 65	126	123 (97.6)	59 (46.8)	5 (4.0)	130	126 (96.9)	64 (49.2)	3 (2.3)
REGION (%)								
NORTH AMERICA	23	23 (100.0)	14 (60.9)	1 (4.3)	21	21 (100.0)	9 (42.9)	0
EUROPE	122	116 (95.1)	49 (40.2)	4 (3.3)	126	122 (96.8)	49 (38.9)	1 (0.8)
ASIA	65	65 (100.0)	37 (56.9)	1 (1.5)	49	48 (98.0)	27 (55.1)	1 (2.0)
REST OF WORLD	18	18 (100.0)	8 (44.4)	1 (5.6)	34	34 (100.0)	14 (41.2)	2 (5.9)
TYPE OF PLATINUM THERAPY (%)								
CISPLATIN	55	55 (100.0)	19 (34.5)	3 (5.5)	42	41 (97.6)	16 (38.1)	1 (2.4)
CARBOPLATIN	167	161 (96.4)	85 (50.9)	4 (2.4)	180	176 (97.8)	79 (43.9)	3 (1.7)
SWITCHING FROM CISPLATIN TO CARBOPLATIN	5	5 (100.0)	3 (60.0)	0	6	6 (100.0)	3 (50.0)	0
NOT REPORTED	1	1 (100.0)	1 (100.0)	0	2	2 (100.0)	1 (50.0)	0

MedDRA Version: 26.0; CTCAE Version: 4.0

Includes events reported between first treatment and 30 days after last treatment of study therapy including definitive surgery and radiotherapy.

Table 64. Drug-Related AEs during the Overall Treatment Period by Worst CTC Grade and by Age, Sex, Race, Region, and Type of Platinum Therapy - All Treated Subjects in the Global Population

	Arm A: Nivo + Chemo / Nivo N = 228				Arm B: Placebo + Chemo / Placebo N = 230			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
OVERALL STUDY POPULATION	**228**	**203 (89.0)**	**74 (32.5)**	**1 (0.4)**	**230**	**200 (87.0)**	**58 (25.2)**	**0**
SEX (%)								
MALE	167	152 (91.0)	52 (31.1)	0	158	139 (88.0)	40 (25.3)	0
FEMALE	61	51 (83.6)	22 (36.1)	1 (1.6)	72	61 (84.7)	18 (25.0)	0
RACE (%)								
WHITE	154	129 (83.8)	37 (24.0)	1 (0.6)	174	146 (83.9)	37 (21.3)	0
BLACK OR AFRICAN AMERICAN	4	4 (100.0)	1 (25.0)	0	4	3 (75.0)	0	0
ASIAN	66	66 (100.0)	35 (53.0)	0	49	48 (98.0)	21 (42.9)	0
OTHER	4	4 (100.0)	1 (25.0)	0	3	3 (100.0)	0	0
AGE (%)								
< 65	102	91 (89.2)	31 (30.4)	0	100	88 (88.0)	18 (18.0)	0
>= 65 AND < 75	114	101 (88.6)	40 (35.1)	1 (0.9)	112	98 (87.5)	33 (29.5)	0
>= 75	12	11 (91.7)	3 (25.0)	0	18	14 (77.8)	7 (38.9)	0
>= 65	126	112 (88.9)	43 (34.1)	1 (0.8)	130	112 (86.2)	40 (30.8)	0
REGION (%)								
NORTH AMERICA	23	22 (95.7)	7 (30.4)	1 (4.3)	21	18 (85.7)	5 (23.8)	0
EUROPE	122	100 (82.0)	29 (23.8)	0	126	107 (84.9)	28 (22.2)	0
ASIA	65	65 (100.0)	34 (52.3)	0	49	48 (98.0)	21 (42.9)	0
REST OF WORLD	18	16 (88.9)	4 (22.2)	0	34	27 (79.4)	4 (11.8)	0
TYPE OF PLATINUM THERAPY (%)								
CISPLATIN	55	50 (90.9)	13 (23.6)	1 (1.8)	42	36 (85.7)	9 (21.4)	0
CARBOPLATIN	167	147 (88.0)	58 (34.7)	0	180	156 (86.7)	46 (25.6)	0
SWITCHING FROM CISPLATIN TO CARBOPLATIN	5	5 (100.0)	2 (40.0)	0	6	6 (100.0)	2 (33.3)	0
NOT REPORTED	1	1 (100.0)	1 (100.0)	0	2	2 (100.0)	1 (50.0)	0

MedDRA Version: 26.0 CTCAE Version: 4.0

Includes events reported between first treatment and 30 days after last treatment of study therapy including definitive surgery and radiotherapy.

Age groups

For subjects treated in the nivo+chemo/nivolumab arm, the rates of all-causality (any-grade) AEs and drug-related (any-grade) AEs reported in older (≥ 65 years) subjects were respectively 97.6% and 88.9%, which was comparable to the rates reported in younger (< 65 years) subjects: 97.1% and 89.2%, respectively. Within the nivo+placebo/nivolumab arm, these rates in the older (≥ 65 years) subjects were also comparable to the rates in the younger (< 65 years) subjects.

For subjects treated in the nivo+chemo/nivolumab arm, the rates of SAEs, fatal AEs, and AEs leading to discontinuation that were reported were generally comparable in older subjects (age ≥65 to < 75 years) compared to younger subjects (age < 65 years; Table 65).

Table 65. Summary of On-treatment Adverse Events by Age Group - All Treated Subjects in CA20977T

Treatment Group: Arm A: Nivolumab 360 mg + Chemotherapy/Nivolumab 480 mg N = 228	Age Group (Years)				
MedDRA Terms (%)	< 65 N = 102	65-74 N = 114	75-84 N = 12	>= 85 N = 0	Total N = 228
TOTAL SUBJECTS WITH AN EVENT	99 (97.1)	111 (97.4)	12 (100.0)	0	222 (97.4)
SERIOUS AE - TOTAL	43 (42.2)	49 (43.0)	4 (33.3)	0	96 (42.1)
FATAL (DEATH)	4 (3.9)	6 (5.3)	1 (8.3)	0	11 (4.8)
HOSPITALIZATION/PROLONGATION	39 (38.2)	44 (38.6)	4 (33.3)	0	87 (38.2)
LIFE THREATENING	7 (6.9)	9 (7.9)	0	0	16 (7.0)
CANCER	4 (3.9)	0	0	0	4 (1.8)
DISABILITY/INCAPACITY	1 (1.0)	0	0	0	1 (0.4)
IMPORTANT MEDICAL EVENT	8 (7.8)	7 (6.1)	0	0	15 (6.6)
AE LEADING TO DISCONTINUATION	22 (21.6)	30 (26.3)	4 (33.3)	0	56 (24.6)
PSYCHIATRIC DISORDERS	15 (14.7)	17 (14.9)	4 (33.3)	0	36 (15.8)
NERVOUS SYSTEM DISORDERS	49 (48.0)	51 (44.7)	8 (66.7)	0	108 (47.4)
ACCIDENT AND INJURIES	4 (3.9)	6 (5.3)	1 (8.3)	0	11 (4.8)
CARDIAC DISORDERS	14 (13.7)	10 (8.8)	1 (8.3)	0	25 (11.0)
VASCULAR DISORDERS	13 (12.7)	15 (13.2)	1 (8.3)	0	29 (12.7)
CEREBROVASCULAR DISORDERS	3 (2.9)	5 (4.4)	0	0	8 (3.5)
INFECTIONS AND INFESTATIONS	45 (44.1)	47 (41.2)	5 (41.7)	0	97 (42.5)
ANTICHOLINERGIC SYNDROME	21 (20.6)	31 (27.2)	5 (41.7)	0	57 (25.0)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	8 (7.8)	12 (10.5)	1 (8.3)	0	21 (9.2)

Treatment Group: Arm B: Placebo + Chemotherapy/Placebo N = 230	Age Group (Years)				
MedDRA Terms (%)	< 65 N = 100	65-74 N = 112	75-84 N = 17	>= 85 N = 1	Total N = 230
TOTAL SUBJECTS WITH AN EVENT	99 (99.0)	108 (96.4)	17 (100.0)	1 (100.0)	225 (97.8)
SERIOUS AE - TOTAL	25 (25.0)	38 (33.9)	8 (47.1)	0	71 (30.9)
FATAL (DEATH)	2 (2.0)	2 (1.8)	1 (5.9)	0	5 (2.2)
HOSPITALIZATION/PROLONGATION	24 (24.0)	37 (33.0)	8 (47.1)	0	69 (30.0)
LIFE THREATENING	2 (2.0)	8 (7.1)	2 (11.8)	0	12 (5.2)
CANCER	2 (2.0)	3 (2.7)	1 (5.9)	0	6 (2.6)
DISABILITY/INCAPACITY	0	0	0	0	0
IMPORTANT MEDICAL EVENT	2 (2.0)	3 (2.7)	3 (17.6)	0	8 (3.5)
AE LEADING TO DISCONTINUATION	8 (8.0)	12 (10.7)	5 (29.4)	0	25 (10.9)
PSYCHIATRIC DISORDERS	13 (13.0)	17 (15.2)	1 (5.9)	0	31 (13.5)
NERVOUS SYSTEM DISORDERS	46 (46.0)	55 (49.1)	7 (41.2)	0	108 (47.0)
ACCIDENT AND INJURIES	4 (4.0)	9 (8.0)	3 (17.6)	0	16 (7.0)
CARDIAC DISORDERS	7 (7.0)	16 (14.3)	1 (5.9)	0	24 (10.4)
VASCULAR DISORDERS	10 (10.0)	17 (15.2)	1 (5.9)	0	28 (12.2)
CEREBROVASCULAR DISORDERS	0	4 (3.6)	0	0	4 (1.7)
INFECTIONS AND INFESTATIONS	36 (36.0)	45 (40.2)	9 (52.9)	0	90 (39.1)
ANTICHOLINERGIC SYNDROME	12 (12.0)	20 (17.9)	3 (17.6)	0	35 (15.2)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	5 (5.0)	12 (10.7)	0	0	17 (7.4)

Includes events reported between first dose and 30 days after last dose of study therapy including definitive surgery and radiotherapy.
MedDRA Version: 26.0; CTC Version 4.0 Includes events reported between first dose and 30 days after last dose of study therapy.

Discontinuation due to adverse events

The proportions of subjects with all causality and drug-related AEs reported as leading to discontinuation of at least 1 study drug were higher in the nivo+chemo/nivolumab arm than the placebo+chemo/placebo arm (Table 66).

There were no subjects in the nivo+chemo/nivolumab arm and 1 subject in the placebo+chemo/placebo arm who had an AE leading to discontinuation reported as a COVID-19 infection.

Table 66. Adverse Events Leading to Discontinuation on Overall Treatment by Worst CTC Grade Reported in at Least 2 Subjects - All Treated Subjects in the Global Population

	Arm A: Nivo + Chemo/Nivo N = 228	**Arm B: Placebo + Chemo/Placebo N = 230**

System Organ Class (%) Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	56 (24.6)	32 (14.0)	0	25 (10.9)	14 (6.1)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	13 (5.7)	6 (2.6)	0	3 (1.3)	2 (0.9)	1 (0.4)
Pneumonitis	6 (2.6)	2 (0.9)	0	2 (0.9)	2 (0.9)	0
Haemoptysis	2 (0.9)	1 (0.4)	0	0	0	0
Interstitial lung disease	2 (0.9)	0	0	0	0	0
Nervous system disorders	11 (4.8)	5 (2.2)	0	4 (1.7)	2 (0.9)	0
Peripheral sensory neuropathy	5 (2.2)	1 (0.4)	0	1 (0.4)	0	0
Neuropathy peripheral	1 (0.4)	0	0	2 (0.9)	2 (0.9)	0
Gastrointestinal disorders	10 (4.4)	4 (1.8)	0	1 (0.4)	0	0
Diarrhoea	3 (1.3)	1 (0.4)	0	0	0	0
Nausea	2 (0.9)	1 (0.4)	0	0	0	0
Renal and urinary disorders	6 (2.6)	2 (0.9)	0	2 (0.9)	1 (0.4)	0
Acute kidney injury	2 (0.9)	2 (0.9)	0	1 (0.4)	1 (0.4)	0
Nephritis	2 (0.9)	0	0	0	0	0
Blood and lymphatic system disorders	2 (0.9)	1 (0.4)	0	3 (1.3)	3 (1.3)	0
Anaemia	1 (0.4)	0	0	3 (1.3)	3 (1.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.9)	0	0	4 (1.7)	2 (0.9)	0
Malignant neoplasm progression	0	0	0	3 (1.3)	1 (0.4)	0

MedDRA Version: 26.0; CTC Version: 4.0

Includes events reported between first treatment and 30 days after last treatment of study therapy including definitive surgery and radiotherapy

Adverse events leading to delay or cancellation of surgery

AEs leading to a delay of surgery, defined as a surgery date occurring > 6 weeks after the last neoadjuvant treatment date were as follows: 3.5% in the nivo+chemo/nivolumab arm and 2.2% in the placebo+chemo/placebo.

Table 67. Any Adverse Event Leading to Definitive Surgery Delay by Worst CTC Grade - All Treated Subjects in the Global Population

System Organ Class (%)	Arm A: Nivolumab + Chemo/Nivo N = 228			Arm B: Placebo + Chemo/Placebo N = 230		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	8 (3.5)	2 (0.9)	0	5 (2.2)	1 (0.4)	0
Respiratory, thoracic, and mediastinal disorders	3 (1.3)	2 (0.9)	0	1 (0.4)	0	0
Acute respiratory failure	1 (0.4)	1 (0.4)	0	0	0	0
Bronchospasm	1 (0.4)	0	0	0	0	0
Hypersensitivity pneumonitis	1 (0.4)	1 (0.4)	0	0	0	0
Pulmonary embolism	0	0	0	1 (0.4)	0	0
Endocrine disorders	1 (0.4)	0	0	0	0	0
Hyperthyroidism	1 (0.4)	0	0	0	0	0
General disorders and administration site conditions	1 (0.4)	0	0	2 (0.9)	0	0
Asthenia	1 (0.4)	0	0	1 (0.4)	0	0
Fatigue	0	0	0	1 (0.4)	0	0
Infections and infestations	1 (0.4)	0	0	1 (0.4)	0	0
COVID-19	1 (0.4)	0	0	1 (0.4)	0	0
Nervous system disorders	1 (0.4)	0	0	0	0	0
Guillain-Barre syndrome	1 (0.4)	0	0	0	0	0
Vascular disorders	1 (0.4)	0	0	0	0	0
Peripheral embolism	1 (0.4)	0	0	0	0	0
Gastrointestinal disorders	0	0	0	1 (0.4)	1 (0.4)	0
Intestinal ischaemia	0	0	0	1 (0.4)	1 (0.4)	0

MedDRA Version: 26.0; CTC Version: 4.0

AEs leading to cancellation of surgery were 3.1% in the nivo+chemo/nivolumab arm and 1.7% in the placebo+chemo/placebo arm (Table 68).

Table 68. Any Adverse Event Leading to Cancellation of Surgery by Worst CTC Grade - All Treated Subjects in the Global Population

System Organ Class (%)	Arm A: Nivolumab + Chemo/Nivo N = 228			Arm B: Placebo + Chemo/Placebo N = 230		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	7 (3.1)	3 (1.3)	1 (0.4)	4 (1.7)	1 (0.4)	1 (0.4)
Cardiac disorders	2 (0.9)	0	0	3 (1.3)	1 (0.4)	0
Acute coronary syndrome	1 (0.4)	0	0	0	0	0
Myocarditis	1 (0.4)	0	0	0	0	0
Atrial fibrillation	0	0	0	1 (0.4)	0	0
Coronary artery disease	0	0	0	1 (0.4)	1 (0.4)	0
Left ventricular dysfunction	0	0	0	1 (0.4)	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.9)	1 (0.4)	1 (0.4)	1 (0.4)	0	1 (0.4)
Haemoptysis	1 (0.4)	1 (0.4)	0	0	0	0
Pneumonitis	1 (0.4)	0	1 (0.4)	0	0	0
Chronic respiratory failure	0	0	0	1 (0.4)	0	1 (0.4)
Gastrointestinal disorders	1 (0.4)	1 (0.4)	0	0	0	0
Colitis	1 (0.4)	1 (0.4)	0	0	0	0
Infections and infestations	1 (0.4)	0	0	0	0	0
Pneumonia	1 (0.4)	0	0	0	0	0
Nervous system disorders	1 (0.4)	1 (0.4)	0	0	0	0
Cerebrovascular accident	1 (0.4)	1 (0.4)	0	0	0	0

MedDRA Version: 26.0; CTC Version: 4.0

Post marketing experience

Based on pharmacovigilance activities, post-marketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab.

2.5.1. Discussion on clinical safety

Safety assessment in the new claimed indication is based on safety data from all 458 subjects who had received at least one dose of any study drug in the neoadjuvant or adjuvant setting who were concurrently randomized to receive nivo+chemo/nivolumab (n=228) and placebo+chemo/placebo (n=230) in the pivotal study CA20977T. At the time of the clinical data cut off (26-Jul-2023), the median follow-up among all randomized subjects was 25.4 months, with a minimum follow-up of 15.7 months. This median follow-up period seems short compared to other studies such as CA209816 (Opdivo II-117), which supported the neoadjuvant treatment indication of resectable NSCLC for nivolumab in combination with chemotherapy, and had a median follow-up of 29.5 months and, also, taken into account the expected total duration of this treatment approach (neoadjuvant for 4 cycles – surgery – adjuvant up to 13 cycles). However, considering that the safety of nivolumab is well known, including for nivolumab treatment in combination with platinum-based chemotherapy, and that only 8 patients were still ongoing adjuvant treatment at the DCO, this median follow-up period is considered sufficient for a safety assessment.

During the procedure, the MAH provided updated safety data with a DCO of 22-Mar-2024. Overall, the updated safety profile was consistent with previously reported data and no new signals were identified.

The safety data referred hereafter correspond to the initial DCO of 26-Jul-2023, unless otherwise specified. Update of the product information is based on the DCO of 22-Mar-2024.

Patient exposure

The median duration of therapy in the overall treatment period was 10.30 months for the nivo/chemo+nivolumab arm and 12.57 months for the placebo/chemo+placebo arm. The median duration of neoadjuvant and adjuvant therapy was the same in both arms (9.14 weeks and 11.07 months, respectively). Therefore, the differences in the median duration of overall treatment period are likely due to the higher number of subjects discontinuing the treatment in the nivo+chemo/nivolumab arm (n = 39) right after surgery vs the placebo+chemo/placebo arm (n = 29).

The proportion of subjects who completed neoadjuvant treatment period was 85.1% in the nivo+chemo/nivolumab arm and 89.1% in the placebo+chemo/placebo arm. In both arms, the main reason for discontinuation of neoadjuvant treatment was study drug toxicity, however, the percentage was higher in the nivolumab arm compared to the placebo arm (9.2% vs 4.8%). The percentage of discontinuations of neoadjuvant treatment is higher in this study (CA20977T) than in Study CA209816 (Opdivo II-117), however this might be due to the additional 4th cycle of neoadjuvant treatment that was administered in study CA20977T.

In the nivo+chemo/nivolumab arm, most subjects received 4 cycles of neoadjuvant treatment (83.8% for nivo; range for the chemo agents: 77.8% - 89.4%), this was similar in the placebo+chemo/placebo arm (89.1% for placebo; range for the chemo agents: 79.2% - 89-1%). Overall, the proportions of subjects with dose modifications of chemotherapy (delay, reduction, interruption, rate reduction, omission) were similar in both treatment arms. The majority of dose delays and reductions were due to AEs, and its incidence and nature seem balanced between treatment arms.

A similar proportion of patients in both arms had definitive surgery (77.7% vs 76.7%), and this suggests that the addition of nivolumab to chemotherapy did not decrease the feasibility of the surgery. However, some differences were observed in the proportion of subjects whose surgery was cancelled due to adverse events (15.2% in the nivolumab arm vs. 8.0% in the placebo arm). The percentage of patients whose surgery was delayed was similar between both arms (20.2% vs 18.5%) and no apparent differences were identified regarding the reasons for delay of surgery between treatment arms. The duration of surgery and length of hospital stay were also similar in the 2 treatment arms, and even though the number of patients who had an ICU stay after surgery was higher in the nivolumab arm than in the placebo arm (90 patients vs 66 patients), the median duration of ICU stay was the same in both arms (2.0 days).

Thirty-nine (39) subjects in the nivo+chemo/nivolumab arm and 29 subjects in the placebo+chemo/placebo arm had definitive surgery but did not receive adjuvant therapy (22% and 16% of the subjects who underwent surgery, respectively). In the nivolumab arm, the most common reason for not receiving adjuvant treatment was study drug toxicity (33.3%), and this percentage is quite significant compared to the placebo arm (17.2%). This observed difference and the slight imbalances in reasons for not receiving adjuvant therapy between arms are considered relevant since these figures could question the perioperative treatment approach if the fact of not receiving adjuvant treatment had any or no impact at all in the patients' outcome. No major differences on the baseline characteristics of patients who underwent surgery but did not receive adjuvant treatment could be identified between both treatment arms. Additionally, adverse events that precluded patients from receiving adjuvant treatment were quite diverse, however considering their nature (for instance, skin toxicity or endocrinopathies) they seem to be mostly related to nivolumab rather than to chemotherapy.

The proportion of patients that completed the adjuvant treatment period was similar in both arms (59.9% in the nivo+chemo/nivolumab arm vs 60.5% in the placebo+chemo/placebo arm). Among subjects who received adjuvant treatment, the main reason for discontinuation of adjuvant treatment in the nivolumab arm was study drug toxicity (12.0% vs 2.0% in the placebo arm) followed by disease progression/recurrence (11.3% vs 24.3% in the placebo arm).

The median number of doses of adjuvant therapy (nivolumab or placebo) was the same in both arms (13.0). In the nivo+chemo/nivolumab arm, dose delays of adjuvant therapy were more frequent compared to the placebo+chemo/placebo arm (38.0% vs 30.9%), and the proportion of subjects with a dose delay > 42 days was also higher in the nivo+chemo/nivolumab arm (11.5% vs 4.9%). AEs as a reason for dose delay were higher in the nivolumab arm compared with the placebo arm (38.5% vs 25.6%).

Adverse events

Almost all patients reported an AE during the overall study treatment: 97.4% in the nivo+chemo/nivolumab arm and 97.8% in the placebo+chemo/placebo arm. By PT, the three most frequent AEs were the same in both arms: "anaemia" (39.5% vs 32.2%), "constipation" (32.0% vs 27.8%), and "nausea" (28.9% vs 34.3%). Overall, the incidence of adverse events was similar in both arms, with some differences observed especially for "hypothyroidism" (11.0 vs 1.7%), "white blood cell count decreased" (12.3% vs 4.3%), "neutrophil count decreased" (16.2% vs 8.7%), "blood creatinine increased" (12.7% vs 5.2%) and "pruritus" (14.0% vs 7.0%), which seemed to be more frequent in the nivolumab arm compared to the placebo arm.

Regarding Grade 3/4 AEs in the overall treatment period, 47.4% of patients reported a G3/4 AE in the nivo+chemo/nivolumab arm vs. 43.0% in the chemo arm. The most frequently reported Grade 3/4 AEs by PT were neutrophil count decreased (10.5%), anaemia (7.9%), and WBC decreased (5.7%) in the nivo+chemo/nivolumab arm and neutrophil count decreased (6.5%), neutropenia (5.7%), and anaemia (4.3%) in the placebo+chemo/placebo arm.

No significant differences were observed between the nature of AEs (regardless of causality) and drug-related AEs in the overall treatment period. Drug-related AEs were similarly reported in both arms (89% vs 87%), however the incidence of G3/4 drug-related AEs was higher in the nivolumab arm than in the placebo arm (32.5% vs 25.2%). The most frequently reported drug-related AEs in the nivolumab arm were anaemia (25.0%), nausea (23.2%), and alopecia (22.8%).

Serious adverse events

The overall frequency of all-causality SAEs was higher in the nivo+chemo/nivolumab arm (42.1%) compared with the placebo+chemo/placebo arm (30.9%), also the percentage of G3-4 SAEs was higher in the nivolumab arm (28.5% vs 20.0%). The most frequently reported SAEs in the nivo+chemo/nivolumab arm were "pneumonia" (3.5%), "haemoptysis" and "pneumonitis" (2.2% each), and in the placebo+chemo/placebo arm, "pneumonia" (3.9%), "pneumonitis", "anaemia" and "atrial fibrillation" (1.7% each). No major differences were observed in the nature of SAEs between both arms, except for AEs belonging to SOC "gastrointestinal disorders" (9.6% vs 3.0%), which were more frequent in the nivolumab arm.

Deaths

A similar proportion of patients died in both arms, although it was slightly lower in the nivo+chemo/nivolumab arm (17.5% vs 20.9%). The number of subjects who died between start of neoadjuvant therapy and 30 days after last dose of neoadjuvant therapy was similar in both treatment arms, although somewhat higher in the nivo+chemo/nivolumab arm (2.2% vs 1.7%). Deaths following surgery were reported in a lower proportion of subjects in the nivo+chemo/nivolumab arm than in the

placebo+chemo/placebo arm (10.1% vs 14.6%). However, the percentage of patients that died within 90 days of surgery was higher in the nivolumab arm compared to the placebo arm (2.2% vs 0.6%), and these deaths were classified as due to "other". Of note, no deaths were reported between the start of adjuvant therapy and 30 days after the last dose of adjuvant therapy in any of the treatment arms.

In the overall treatment period, disease progression was the primary reason for death in both arms (9.2% for nivolumab vs. 17.0% for placebo). Sixteen patients in the nivo+chemo/nivolumab arm died due to "other" reasons, mostly due to infections (including "septic shock", "COVID-19", "pneumonia", "pneumonia pseudomonal" and "ventilator associated pneumonia") and cardiovascular events (including "cerebrovascular accident", "cardiac arrest", "ischemic stroke", "acute myocardial infraction", "sudden death" and "cerebral infraction"). It cannot be excluded that these deaths occurred partially due to nivolumab, even though they were considered not related to the study drug by the investigator.

Two deaths due to study drug toxicity were reported in the nivo+chemo/nivolumab arm. Both subjects died due to pneumonitis after completing 4 cycles of neoadjuvant treatment but before surgery, and the deaths occurred 28 days and 154 days after the last dose of nivolumab (neoadjuvant). No deaths due to study drug toxicity were reported in the placebo+chemo/placebo arm.

The proportion of patients who had an adverse event leading to death in the overall treatment period was higher in the nivolumab arm compared to the placebo arm (7.0% vs 5.2%). Although no solid conclusions can be drawn due to the low number of events, it seems that AEs leading to death in the nivolumab arm are infection-related; whereas in the placebo arm, most AEs leading to death pertain to SOC "Respiratory, thoracic and mediastinal disorders".

Other significant events

The proportion of any grade drug-related **select AEs** was higher for all categories in the nivo+chemo/nivolumab arm compared to the placebo+chemo/placebo arm. Among all categories, the frequency of any-grade "endocrine", "skin", and "renal" were at least 7% higher in the nivolumab arm compared to the placebo arm. The majority of select adverse events were reported to have resolved by the DBL, however, endocrine select AEs was the category with the lowest proportion of resolved events (57.6% in the nivolumab arm). It is acknowledged that patients with endocrine AES take long time to recover (median time to resolution: 22.3 weeks according to data provided), also due to the continuing need for hormone replacement therapy, and this is in line with data previously reported for nivolumab.

The frequency of **all-causality IMAEs** was higher in the nivo+chemo/nivolumab arm compared to the placebo+chemo/placebo arm, and differences were observed especially for "hypothyroidism/thyroiditis" (11.0% vs 1.7%) and "pneumonitis" (5.3% vs 1.3%). In the overall treatment period, pneumonitis was the IMAE that most frequently led to discontinuation of study treatment (4.4% of patients), and 4 subjects (2.2%) had a G3-4 pneumonitis. Nevertheless, the majority of IMAEs were Grade 1-2 and were manageable using the established management algorithms. Only 44% of hypothyroidism/thyroiditis and 58.3% of pneumonitis in the nivo+chemo/nivolumab arm were considered resolved at the time of the DBL. At the DCO of 22-Mar-2024, 24/25 subjects in the nivo+chemo/nivolumab arm still had ongoing events, and 76% of them belonged to endocrine categories.

OESIs (all causality, with or without IMM treatment), with extended follow-up, were reported in 4 subjects (1.8%) in the nivo+chemo/nivolumab arm (pancreatitis, Guillain-Barre Syndrome, and myositis reported in 1 subject each and 1 subject with myositis, myocarditis and immune-mediated myocarditis) and in 1 (0.4%) subject in the placebo+chemo/placebo arm (pancreatitis). Most OESIs were resolved (4/6 in the nivo+chemo/nivolumab arm and 1/1 event in the placebo+chemo/placebo arm).

Of note, all OESIs that were reported in the nivo+chemo/nivolumab arm occurred during the neoadjuvant phase. On the contrary, no OESIs were reported in the control arm during the neoadjuvant phase, and the only OESI reported in this arm occurred during the adjuvant phase. The MAH was invited to provide information on the outcome of these 4 patients in the nivolumab arm that had an OESI during the neoadjuvant phase. During the procedure, the MAH indicated that at the new DCO of 22-Mar-2024, 2/4 OESIs that were reported during the neoadjuvant phase were still ongoing, one being a Grade 2 serious Guillain-Barre syndrome and the other a serious pancreatitis. The other two cases (one myositis and one immune-mediated myocarditis) had resolved.

Surgical complications

Regarding surgical complications, 41.0% of patients in the nivo+chemo/nivolumab arm reported an event of any grade identified as a surgical complication vs. 38.8% in the chemo+placebo/chemo arm; however the frequency of G3-4 events was the same in both arms (11.8%). Overall, the percentage of AES reported as surgical complications were similar in both arms, however, any-grade AEs belonging to "Injury, poisoning and procedural complications" SOC were reported with a higher frequency in the nivolumab arm (16.9% vs 11.8%).

Discontinuation due to AEs

The proportion of subjects with any-grade all-causality AEs leading to discontinuation of treatment was higher in the nivo+chemo/nivolumab arm than in the placebo+chemo/placebo arm (24.6% vs 10.9%). The proportion of G3-4 AEs leading to discontinuation was also higher in the nivolumab arm (14.0% vs 6.1%). In the nivolumab arm, the most common reported AEs leading to discontinuation were pneumonitis (2.6%), peripheral sensory neuropathy (2.2%), and diarrhoea (1.3%); whereas in the placebo arm, they were anaemia and malignant neoplasm progression (1.3% each).

The frequency of any-grade AEs that led to a delay of surgery (surgery occurring > 6 weeks after the last neoadjuvant) was 3.5% in the nivo+chemo/nivolumab arm and 2.2% in the placebo+chemo/placebo arm. The proportion of G3-4 AEs that led to delay of surgery was overall low and similar in both arms (0.9% vs 0.4%). AEs that led to a delay of surgery belonging to "Respiratory, thoracic, and mediastinal disorders" SOC were the most common reported in the nivolumab arm (1.3%).

The proportion of all-grade AEs leading to cancellation of surgery were 3.1% in the nivo+chemo/nivolumab arm and 1.7% in the placebo+chemo/placebo arm, also the frequency of G3-4 AEs that led to surgery cancellation was slightly higher in the nivolumab arm (1.3% vs 0.4%). In both arms, the most frequently reported AEs leading to surgery cancellation belonged to "cardiac disorders" SOC (0.9% vs 1.3%), followed by "Respiratory, thoracic and mediastinal disorders" SOC (0.9% vs 0.4%).

Laboratory findings

Laboratory abnormalities (haematology, liver tests, kidney function tests, thyroid function tests, and electrolytes) were primarily Grade 1-2 in severity. "Haemoglobin" was the laboratory parameter for which most alterations were reported: 75.8% in the nivo+chemo/nivolumab arm and 67.3% in the placebo+chemo/placebo arm, followed by "absolute neutrophil count" (52.5% vs. 42.9%) and "lymphocytes" (46.2% vs 35.0%). For the remaining laboratory parameters, the incidences of all-grade events in both arms were overall similar, except for "alanine aminotransferase" (36.3% vs 23.2%), "aspartate aminotransferase" (32.7% vs 22.2%), "leukocytes" (40.4% vs 34.1%), "creatinine" (33.6% vs 25.7%) and "hyperkalaemia" (27.8% vs 19.9%), which were higher in the nivo+chemo/nivolumab arm.

Abnormalities in liver function tests were more frequently reported in the nivo+chemo/nivolumab arm. Two subjects in the nivo+chemo/nivolumab arm (and none in the placebo arm) were reported with concurrent ALT or AST > 3 x ULN with total bilirubin > 2 x ULN within 30 days of last dose of study therapy; thus meeting the biochemical criteria for Hy´s law. However, none of these two patients died from drug-induced liver injury and they both entered into survival follow-up.

TSH increases (> ULN) from a baseline level ≤ ULN were reported in 23.1% of subjects in the nivo+chemo/nivolumab arm and 9.8% of subjects in the placebo+chemo/placebo arms; whereas TSH decreases (< LLN) from a baseline level ≥LLN were reported in 17.6% and 12.1% of subjects, respectively. Regarding electrolyte levels, even though "hyperkalaemia" was more frequently reported in the nivolumab arm than in the placebo arm (27.8% vs 19.9%), most alterations were similar in frequency and grade in both treatment arms, and primarily Grade 1-2. G3-4 hyperglycaemias were also more frequently reported in the nivolumab arm than in the placebo arm (5.3% vs 0.9%).

Baseline vital signs and changes from baseline were balanced between treatment arms and no relevant differences could be identified.

Safety in special populations

Regarding safety in special populations, reported AEs were, in general, comparable between treatment arms. The frequency of G3-4 AEs in females was higher in the nivo+chemo/placebo arm than in the placebo+chemo/placebo arm (all causality: 45.9% vs 38.9%; drug related: 36.0% vs 25.0%). Other small differences were observed in the frequency of all-causality and drug-related AEs, however, it is difficult to draw conclusions since the sample size of subgroups is quite small. Regarding age-groups, even though the number of patients between 75-84 years old is limited (12 patients in the nivo+chemo/nivolumab arm and 17 patients in the placebo+chemo/placebo arm), it is considered relevant in this early-stage disease setting where enrolled patients needed to be eligible for surgery. Only one patient >85 was enrolled (in the placebo arm), therefore no data are available for this subgroup. Information on the proportion of patients ≥75 years has been included in section 5.1 of the SmPC.

Immunogenicity

The proportion of subjects with nivolumab ADA at baseline (5.1%) and post-baseline (12.1%) was low and did not appear to affect the efficacy or safety of nivo+chemo/nivo. One of the 198 ADA positive subjects (0.5%) was neutralizing ADA positive. The MAH updated the information on Immunogenicity of section 4.8 of the SmPC with the latest data.

Safety data to support the PI

Regarding section 4.8 of the SmPC, the results from study CA20977T were incorporated to the nivolumab+chemotherapy pooled dataset (that included studies CA209648, CA209649, CA209816 and CA209901), and this approach is endorsed. Overall, the updates proposed in section 4.8 of the SmPC have been appropriately justified.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of nivolumab with platinum-containing chemotherapy as neoadjuvant treatment, and then as monotherapy as adjuvant treatment, results in a worse safety profile that combines the already known toxicities for both nivolumab and chemotherapy.

Significantly higher incidences of SAEs and AEs leading to discontinuation have been reported in the nivolumab arm compared to placebo, also the frequency of IMAEs was higher in the nivolumab arm than in the placebo arm. Nevertheless, the nature of AEs seems to be consistent with the known safety

profile of nivolumab+chemotherapy, and no new safety signals have been identified.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated Risk Management Plan (RMP) version 36.0, with data lock point 26-Jul-2023, with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the Risk Management Plan version 36.3 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 36.3 with the following content:

Safety concerns

Table 69. Summary of Safety Concerns

Important identified risks	Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)
	Severe infusion reactions
Important potential risks	Embryofoetal toxicity
	Immunogenicity
	Risk of GVHD with Nivolumab after allogeneic HSCT
Missing information	Patients with severe hepatic and/or renal impairment
	Patients with autoimmune disease
	Patients already receiving systemic immunosuppressants before starting nivolumab
	Long-term safety in adolescent patients ≥ 12 years of age

Pharmacovigilance plan

Table 70. Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
None				
Category 3 - Required additional pharmacovigilance activities				
Long-term follow-up of ipilimumab, nivolumab and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the DMTR (CA184557)[a] Voluntary PASS Planned	To assess safety and long-term outcomes in children and adolescents.	Long-term safety in adolescent patients ≥ 12 years of age	1. Submission of protocol[a] 2. Interim Study Report 3. Final report of study results	Q4 2023 Q4 2026 Q4 2033

Risk minimisation measures

Table 71. Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: Patient Alert Card	Additional pharmacovigilance activities: None
Severe Infusion Reactions	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Embryofoetal toxicity	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimisation measures: SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimisation measures: SmPC Section 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Patients with severe hepatic and/or renal impairment	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimisation measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimisation measures: SmPC Sections 4.4 and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Long-term safety in adolescent patients ≥ 12 years of age	Routine risk minimization measures: SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: Long-term follow-up of ipilimumab, nivolumab, and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the DMTR (CA184557).

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found <acceptable> <unacceptable> for the following reasons:

- The readability of the PL (QRD template Version 9.0) of Opdivo (nivolumab), in English, was assessed during the review of the initial Marketing Authorisation Application (MAA) according to the methods outlined in the European Commission's guideline titled: *A guideline on the readability of the label and package leaflet of medicinal products for human use, Revision 1, 12 January 2009*. The final report was then submitted to the EMA on 02 September 2014 as part of the initial MAA dossier (EMEA/H/C/3985, MAA approved on 19 June 2015).
- The new indication in adults that is hereby applied for concerns the same route of administration and has a similar safety profile as the previously approved indications.
- Administration of Opdivo (nivolumab) is done by a health care professional. The instructions for dose calculation, preparation, administration, storage and disposal that are currently reflected in the approved PL were also successfully tested as part of the user consultation performed for

the initial MAA and remain unchanged.

- The general design and layout of the proposed PL have not changed compared to the tested one.
- Overall, the proposed leaflet shares large text sections with the reference one. The modifications now proposed in the PL do not represent major changes.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

OPDIVO, in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD L1 expression ≥ 1% (see section 5.1 for selection criteria).

The initially sought indication by the MAH encompassed patients regardless of PD L1 expression.

3.1.2. Available therapies and unmet medical need

The standard approach for patients with stage II/III resectable NSCLC is potentially curative surgery followed by adjuvant chemotherapy. According to ESMO Guidelines, adjuvant chemotherapy is of benefit for patients with stage II and III disease, resulting overall in 4%–5% absolute survival improvement at 5 years. Although neoadjuvant chemotherapy has not been evaluated as extensively as postoperative, comparing outcomes of both modalities did not reveal a major difference in OS (ESMO 2017).

Despite adjuvant/neoadjuvant treatment, the recurrence rate remains high, ranging from 62% in patients with Stage II and 76% of patients with Stage III disease (Pignon et al 2008), which in turn is associated with poor survival rates in this patient population (Goldstraw et al 2016). The prevention of disease recurrence and distant metastases, and subsequent progression to an incurable disease state, is therefore critical to improving long-term patient outcomes (Consonni et al 2015).

The addition of anti-PD-1/PD-L1 inhibitors across the neoadjuvant and adjuvant phases of treatment to resectable NSCLC has shown EFS and DFS benefits, respectively, leading to approval in the EU of nivolumab (neoadjuvant setting, PD-L1≥1%), atezolizumab (adjuvant setting, PD-L1 ≥50%), and pembrolizumab (adjuvant setting, PD-L1 unrestricted). Moreover, the CHMP also adopted a positive opinion for the approval of pembrolizumab and durvalumab in the neoadjuvant + adjuvant setting, both of them PD-L1 unrestricted.

Nevertheless, despite the improved efficacy demonstrated in resectable NSCLC with either the neoadjuvant or the adjuvant setting, there is a need to further improve clinical outcomes in this population.

3.1.3. Main clinical studies

The pivotal study for the extension of indication for nivolumab is study CA20977T, a phase III, randomised, multi-centre, double-blind, placebo-controlled study comparing nivolumab 360 mg or placebo Q3W in combination with platinum-based chemotherapy (4 cycles) followed by adjuvant treatment with nivolumab monotherapy 480 mg or placebo Q4W (13 cycles). The ITT population was constituted by 461 patients, who were recruited between 2019 and 2022.

The primary endpoint was EFS by BICR, and the secondary endpoints were OS, pCR by BIPR and MPR by BIPR. Patients were stratified by tumour histology (squamous vs. non-squamous), NSCLC stage (II vs. III), and PD-L1 status (≥1% vs. <1% vs. indeterminate/not evaluable).

3.2. Favourable effects

The interim analysis (IA) for EFS (DCO: 26-Jul-2023) was conducted at 189 EFS events (IF: 81.8%), with a median follow-up of 25.4 months.

- Primary endpoint: EFS by BICR met the boundary for statistically significance in the ITT at the pre specified IA [HR: 0.58 (97.36% CI 0.42, 0.81); p-value: 0.00025]. There were 76 events (33.2%) in the nivolumab arm vs. 113 events (48.7%) in the placebo arm. Median EFS was 18.43 (95% CI: 13.63, 28.06) months in the placebo arm, while it was not reached (95% CI: 28.94, NA) in the nivolumab arm.

At the updated EFS analysis (DCO: 11-Nov-2024), with a median follow-up of 41 months

- In the subgroup of patients with tumour PD L1 expression ≥ 1% (n=128 in both arms), the EFS HR was 0.53 (95% CI: 0.36, 0.76), with 47 events (37%) in the nivolumab arm, and 70 (55%) in the control arm, and median EFS of 46.55 (35.81, NE) and 15.08 months (9.33, 31.41), respectively.
- Secondary endpoint: OS did not reach statistical significance at the OS IA in the ITT [DCO: 11-Nov-2024, 140 events (80% IF)], the HR point estimate was 0.85 (97.63% CI: 0.58, 1.25; 95% CI: 0.61, 1.18).
- In the subgroup of patients with tumour PD L1 expression ≥ 1%, the OS HR was 0.61 (95% CI: 0.39, 0.97), with 31 events (24%) in the nivolumab arm, and 46 (36%) in the control arm, and the median OS was not reached in any arms, the lower bound of the 95%CI was 38.08 months in the placebo arm.

3.3. Uncertainties and limitations about favourable effects

- The study as it was designed does not allow disentangling the contribution of nivolumab to each treatment phase, and whether the administration of nivolumab only in any of the two phases (i.e., as neoadjuvant treatment or as adjuvant treatment) would have resulted in similar clinical outcomes without exposing patients to unnecessary toxicity.
- At the initial DCO, only around 40% (37% of patients in the nivolumab arm and 40% in the placebo arm) of patients who were randomized completed the neoadjuvant + adjuvant treatment. These low completion percentages put into question the feasibility of the proposed regimen.
- Despite a maturity of OS data sufficient to rule out a detrimental effect, long term outcomes in terms of OS are deemed key to the benefit risk in the context of patients who are receiving treatment with a curative intent. Thus, in order to further characterise the efficacy of nivolumab in

the approved indication, results from the final OS analysis will be submitted by Q2 2027 (see Annex II condition, PAES).

3.4. Unfavourable effects

In Study CA20977T, all-causality AEs were similarly reported in both arms (97.4% vs 97.8%). The three most common AEs in both arms by PT, were "anaemia" (39.5% vs 32.2%), "constipation" (32.0% vs 27.8%), and "nausea" (28.9% vs 34.3%). In the nivo+chemo/nivolumab arm, 47.4% of patients reported a G3-4 AE vs. 43.0% in the placebo+chemo/placebo arm, being "neutrophil count decreased" the most common in both arms (10.5% vs 6.5%). Of note, the incidence of G3-4 drug-related AEs was higher in the nivo arm compared with the control arm (32.5% vs. 25.2%).

SAEs were more frequently reported in the nivo+chemo/nivolumab arm (42.1%) compared with the placebo+chemo/placebo arm (30.9%). No major differences were observed in the nature of SAEs between both arms, except for SAEs belonging to SOC "gastrointestinal disorders" (9.6% vs 3.0%), which were more frequently reported in the nivolumab arm.

Two deaths (0.9%) due to study drug toxicity (pneumonitis) were reported in the nivo+chemo/nivolumab arm, while none in the placebo+chemo/placebo arm.

The frequency of all-causality IMAEs was higher in the nivo+chemo/nivolumab arm than in the placebo+chemo/placebo arm, with differences observed especially for "hypothyroidism/thyroiditis" (11.0% vs 1.7%) and "pneumonitis" (5.3% vs 1.3%)

AEs leading to discontinuation of treatment were more frequent in the nivo+chemo/nivolumab arm than in the placebo+chemo/placebo arm (24.6% vs 10.9%), and the most common AEs leading to discontinuation in the nivolumab arm were pneumonitis (2.6%), peripheral sensory neuropathy (2.2%), and diarrhoea (1.3%)

3.5. Uncertainties and limitations about unfavourable effects

No safety data is available for patients >85 years old, and limited data are available for patients between 75 and 84 years old.

3.6. Effects Table

Table 72. Effects Table for nivolumab in combination with chemotherapy in the perioperative setting of NSCLC (data cut-off: 26-Jul-2023)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects (PD-L1 ≥ 1%)			**N=128**	**N=128**		
EFS by BICR in PD-L1 ≥ 1%	Event-free survival	Months (95% CI)	NA (28.94, NA)	15.80 (9.33, 35.06)	Primary EFS analysis in ITT reached statistical significance at pre planned IA. Subgroup analysis not adjusted for multiplicity. Maturity: 40% of EFS events in the selected sub population Median follow-up of 25.4 months (range: 15.7-44.2 months	CSR
		HR (95%CI)	0.52 (95% CI: 0.35, 0.78)			
OS in PD-L1 ≥	Overall	Months	NA	NA (38.08,	Subgroup analysis not	CSR

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
1% [DCO: 11-Nov-24]	survival	(95% CI)		NA)	adjusted for multiplicity Primary OS analysis in ITT did not reach statistical significance at IA; Maturity: 30% of events in the selected sub population Minimum follow-up of 31.3 months	
		HR (95%CI)	0.61 (95% CI: 0.39, 0.97)			
Unfavourable Effects (safety set)			**N=228**	**N=230**		
Grade 3-4 AEs	All causality (drug-related)	%	47.4% (32.5%)	43.0% (25.2%)		CSR
SAEs	All causality (drug-related)	%	42.1% (19.3%)	30.9% (9.6%)		
AEs leading to discontinuation	All causality (drug-related)	%	24.6% (19.3%)	10.9% (7.4%)		
AE leading to deaths	All causality	%	7%	5.2%		

Abbreviations: AE: adverse event; SAE: serious adverse event.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

CA20977T study met its primary endpoint (EFS by BIRC) with statistically significant results for nivolumab in combination with chemotherapy as neoadjuvant treatment and continued as single agent as adjuvant treatment, compared with neoadjuvant chemotherapy plus placebo followed by adjuvant placebo.

EFS met the prespecified boundary for declaring statistically significance at its IA, which was therefore considered the primary analysis. The EFS results showed benefit from nivolumab across the different subgroups of the ITT population, including in patients with PD-L1≥ 1% expression, which was supported by a clear separation of KM curves at around month 3. The maturity of data (IF: 81.8%; FU: 25.4 months) is considered sufficient to assess the benefit in terms of EFS. An updated EFS analysis with longer follow-up (DCO: 11-Nov-2024) showed similar results.

Discarding a detrimental OS effect is considered critical in this potentially curative setting. The pre-planned interim analysis for OS in the ITT (140 events, 80% IF of the final analysis), did not reach statistical significance. The main reason for censoring in both arms was that patients were in follow-up (66.8 % in the nivolumab arm vs. 59.9 % in placebo arm).

Importantly, the results of the OS subgroup analyses did not allow to rule out a detrimental effect in patients with PD-L1 expression <1%. A lower effect was also observed in terms of EFS, pCR, MPR and ORR in this subgroup of patients. While it is acknowledged that OS was a secondary endpoint of the study, not being able to discard a detrimental OS effect in the subgroup of patients with a lower PD-L1 expression (40% of the patient population) is of concern, particularly considering the added toxicity of nivolumab and the need for a longer treatment exposure. Thus, in view of these results, the indication was restricted to patients with a PD-L1≥ 1% expression, in whom benefit seems to be clearly established. In this subgroup an EFS benefit was also clearly established, as well as in the other secondary endpoints.

Although at this point the maturity of the OS results is considered robust enough as to conclude on a positive B/R in patients with a PD-L1≥ 1% expression, in order to further characterise the long-term OS benefit the MAH has committed to submit the final OS analysis, listed as an annex-II condition (**ANX**).

Significantly higher incidences of SAEs, IMAEs and AEs leading to discontinuation have been reported in the nivolumab arm compared to placebo. Nevertheless, the nature of AEs seems to be consistent with the known safety profile of nivolumab+chemotherapy, and no new safety signals have been identified.

3.7.2. Balance of benefits and risks

The efficacy in terms of EFS was demonstrated in the patients whose tumours have PD L1 expression ≥ 1%. In this patient population a detrimental effect on OS could be ruled out.

The efficacy in terms of EFS was demonstrated in the overall population. However, a potential detrimental effect on OS in patients with PD-L1 expression <1% could not be discarded. Thus, uncertainties remain with regard to the benefit of this new treatment regimen in the overall population, leading to the restriction of the indication to patients with a PD-L1 ≥ 1% expression.

The higher incidences of SAEs, IMAEs and AEs leading to discontinuation reported in the nivolumab arm compared to placebo is considered to be outweighed by the improvement in EFS, thus the benefit/risk balance is considered positive in the finally applied indication.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Opdivo is positive.

The following measures are considered necessary to address issues related to efficacy:

Annex II.D Condition: PAES: In order to further characterise the long-term efficacy of OPDIVO in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment, for the treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD L1 expression ≥ 1%, the MAH should submit the results of the final OS analysis from study CA20977T, a phase III, randomised, double-blind study.

With a due date by 30th June 2027.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include OPDIVO in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by monotherapy as adjuvant treatment, for the treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%, based on results from study CA209977T; a phase 3, randomised, double-blind study. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 36.3 of the RMP has also been approved.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post authorisation efficacy study (PAES): In order to further characterise the long-term efficacy of OPDIVO in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by OPDIVO as monotherapy as adjuvant treatment, for the treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD L1 expression ≥ 1%, the MAH should submit the results of the final OS analysis from study CA20977T, a phase III, randomised, double-blind study.	By 30th June 2027